Title
Mapping a Chemical Journey through the United States Chemical Management System

Author
Shen, Beverly

Publication Date
2019

Peer reviewed|Thesis/dissertation

Mapping a Chemical Journey through the United States Chemical Management System

By

Beverly Shen

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Environmental Health Sciences

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:
Professor S. Katharine Hammond, Chair
Professor Asa Bradman
Professor Alan Hubbard

Fall 2019

Mapping a Chemical Journey through the United States Chemical Management System

Beverly Shen

Abstract

Mapping a Chemical Journey through the United States Chemical Management System

by

Beverly Shen

Doctor of Philosophy in Environmental Health Sciences

University of California, Berkeley

Professor S. Katharine Hammond, Chair

Since the phase-out of the historically-used polybrominated diphenyl ethers because of growing evidence of their negative health and environmental impacts, current-use organophosphate flame retardants have re-emerged to replace polybrominated diphenyl ethers. However, very little is known about organophosphate flame retardants. This process of replacing suspected harmful chemicals with understudied alternatives is common. Many chemicals are largely unstudied before they are introduced to consumer products and the environment, and are unregulated. Scientific research has revealed potential negative associations between health and certain chemicals, such as flame retardants. Subsequently, these chemicals are either banned or phased out. Other chemicals with unknown health repercussions potentially replace their banned or phased out predecessors (legacy chemicals) and are often structurally similar to the previous iteration or are structurally similar to other chemicals with adverse impacts on health.

This dissertation maps a typical chemical's path within the United States chemical management system. I chart this process, focusing on flame retardants, by measuring the level of contamination of the legacy flame retardants, polybrominated diphenyl ethers, and the re-emerging organophosphate flame retardants in fire station dust across the United States. Then, I evaluate the association between maternal urinary levels of organophosphate flame retardant metabolites and their effect on sex hormones in male children at age 12. Finally, I present what the electronics industry is currently doing to avoid regrettable substitutions and discuss the need to combine risk assessments with alternatives assessments.

Table of Contents

Acknowledgements

Thank you to my advisor, Kathie Hammond, for taking a chance on me and never giving up on me. I made it to this day because you pushed me to be the researcher I am today. Thank you for challenging me, supporting me, talking me down, and helping me to see both the bigger picture and the smallest of details. My dissertation also greatly benefitted from my committees – thank you to Asa Bradman for connecting me with data for Chapter 3, and for making me think the hardest I have ever thought about cancer slopes; thank you to Alan Hubbard for all the statistical guidance and for telling me to keep statistics simple; thank you to Tom McKone for the life cycle assessment discussions; thank you to John Balmes for giving me points for all the questions I answered correctly before my qualifying exam and for being a Warriors fan. Mark Nicas taught me exposure assessment, for which I will be eternally grateful, but also counseled me through my transition back to Berkeley with much appreciated sarcasm and humor. I am also thankful for Todd Whitehead for always believing in me and for being such a great co-author.

Much of my research came from collaborating with the California Department of Toxic Substances Control. Thank you to Myrto Petreas, June-Soo Park, Reber Brown, Joginder Dhaliwal, and Ranjit Gill for the critical eyes, lab assistance, laughs, and endless support, and for putting me in touch with Sharyle Patton and the International Association of Fire Fighters who allowed me into their community. Thank you also to CHAMACOS, Kim Harley, Brenda Eskenazi, and the Clean Electronics Production Network.

I am also incredibly thankful for the DREAM office for creating the space I needed on campus and for being such a supportive network of beautiful people. Thank you to Debbie Kim, Juan Carlos Piña, Lily Calleros, Lo Hampton, Fiona Diec, Ben Chen and many others at the DREAM office, but especially to Durrain Ansari-Yan and Michelle Azurin for putting up with my crazed fall semester self these last two years, keeping me fed, and reminding me to self-care.

I could not have reached the finish without the unwavering support and humor of my friends and family. I am grateful for the amazing friends I made throughout my graduate career – Mai Fung, GG, who has provided endless entertainment and companionship over the interwebs in the form of predicting plot twists to horror movies; Lauren Baehner, the best housemate I ever had, who never backs down from second breakfasts, lunches, dinners, and desserts; Julia Varshavsky who is the best commiseration partner and would not let me give up; Ledor Igboh who is always game to meet me in another country to catch up; Kat Navarro, Nina Townsend, and Kristen Shive for the unforgettable outdoor adventures; Jen Wang, Erin Milner, Nick Lam, Kathy Tran, Yukiko Yano, Jessica Yuh for all the encouragement and fun times; and Jessica Trowbridge and Rachel Sklar who kept me afloat in the final stretch. Thank you, JTrow, for always being able to keep me from the edge, and Sklar for fighting for our desk space and making me work from campus on December 2, 2019. I will be forever indebted to DtR. I am also thankful for my friends and housemates, Alain Orta-Larsen and Abdul Faqir, for taking the brunt of housework and always saving the last fry or sandwich for me; for my wonderful friends Jacques Wilson and Audrey Toda who are always there for me in ways I don't even know I need; and for Judy Park, the OG GG, for always reminding me to apply sunscreen and promising to keep me in line as I embarked on this journey. And finally, but never least, I am forever grateful to my family – to Uncle David, Gan Die, and Gan Ma for great food, great drink, and great company both stateside and across the Pacific; to Jon Yang and Christina Nguyen for continuing the long tradition of movie-watching and snacking marathons, and for my godsons; to Vicki Yang for exploring the sociological aspects of our motherland with terrible television, and to Brandon Cruse for humoring us; to Evelyn Shen, my little sister who never fails to make me see reality; and to my parents, Pei-Jen and Dih-Fen Shen, for being my greatest critics and my greatest supporters.

We did it.

Chapter 1 – Introduction

1.1 Dissertation overview

This dissertation traces a chemical journey through the United States chemical management system. The research presented within captures the consequences of failing to follow the precautionary principle, which proposes that preventative measures should be implemented when an activity or policy increases risk of harm to human health or the environment even when effects are unknown.[1] My research maps this chemical journey in sequential stages beginning with the phase-out of a chemical (Chapter 2), to the reemergence of a replacement chemical (Chapter 3), and ending with practices to appropriately assess chemical substitution (Chapter 4).

1.2 Flame retardants

Flame retardant chemicals are synthetic chemicals used to delay the ignition of fires. They are commonly used in materials such as building insulation, electronics, and furniture. Many flame retardants are not chemically bound to their final products and can easily escape into the environment.[2] Widespread use of polybrominated diphenyl ethers (PBDEs) in the United States began in the 1970s. Voluntarily phase-out of PBDE use in the United States began in the 2000s as Europe banned their use and concern over their persistence,[3,4] bioaccumulative,[4–6] and toxic properties grew. Research associated exposure to PBDEs with reproductive issues in women[7,8] and men,[9,10] and more recently, diminished neurodevelopment in children.[11–16] PBDEs have been widely used in the United States and though their use has been phased-out as a result of European and Californian regulatory action, they are persistent organic contaminants that migrate to indoor environments and outdoor environments.[17] They have been found in indoor air,[18] indoor dust,[19,20] and food.[21,22] The commercial use of organophosphate flame retardants (PFRs) has increased as an alternative to PBDEs.[23] PFRs have also been found in indoor air[24] and indoor dust.[25] PFR animal toxicity research suggests associations with endocrine disruption[26,27] and at least one PFR, tris(1,3-dichloro-2-propyl)phosphate (TDCPP), is carcinogenic to humans.[23,28] Flame retardants are ubiquitous and PBDEs have generally been found at higher levels in the air and dust of workplaces than in residential homes.[17] For example, high PBDE concentrations have been found in the dust of electronic waste recycling facilities[29] and offices.[30] Likewise, PFRs have been found in higher concentrations in the dust of electronic waste recycling facilities and in homes near electronic waste sites compared with homes far from electronic waste sites.[31]

1.2.1 Flame retardants and firefighters

PBDEs have also been found at comparably higher levels in Southern California fire station dust than in other occupational settings and residential homes.[32] Similarly, high PBDE concentrations have been found in the serum of firefighters from Northern and Southern California as compared to non-Californian firefighters[33] and NHANES.[34] The sources of these high PBDE levels in the firefighter work environment and firefighter serum are still unknown though some studies have postulated that track-back from fire suppression sites[32] and cleanliness of turnout gear[34] could be potential sources for the high levels seen in dust and serum, respectively.

Firefighting remains a dangerous occupation with firefighters experiencing a wide range of occupational health hazards, from ergonomic hazards[35–37] to post-traumatic stress[37–40] to overexertion.[35] They are also exposed to a wide range of chemicals during fire suppression, active extinguishing of fires,[41–47] and fire overhaul, which involves searching for hidden fires among debris left after fire suppression.[48–51] While firefighters are exposed to many occupational hazards, physical and chemical alike, during fire suppression and overhaul, they also spend a lot of on-shift time at their fire stations where a similar exposure scenario to flame retardants exists as that for residents at home. However, elevated PBDE concentrations found in the California fire stations[32] and in firefighter serum[33,34] suggest that firefighters are potentially exposed to higher levels of flame retardants than the general population.

While injuries associated with physical effort, such as ergonomic issues and overexertion, persist as threats to firefighters, chronic illnesses that may be associated with firefighting also compromise firefighter health. Studies examining the relationship between firefighting and cancer cases have found that firefighting may lead to an increased risk in several cancers including lung,[52] leukemia,[52] testicular,[53–55] prostate,[54,55] multiple myeloma,[54] and malignant mesothelioma.[56] Though these epidemiological studies elucidated cancer risk associated with firefighting, they did not measure chemical exposures; instead, they measured surrogates of firefighting exposure, such as total days and hours spent firefighting. Surrogates of firefighting exposure are informative in their own right, but assessing chemical exposures experienced by firefighters could further inform epidemiological studies focusing on incidences of cancer, particularly because firefighters are exposed to known carcinogens such as polycyclic aromatic hydrocarbons (PAHs), benzene, and formaldehyde, during fire suppression and overhaul.[46,49] The time spent at work for a firefighter not only includes fire suppression and fire overhaul, but also on-shift downtime spent at the fire station. Fire station dust has been shown to contain high levels of PBDEs.[32] The high levels of PBDEs found in firefighter serum[33,34] also highlight exposures that may lead to health endpoints that are non-cancerous. Understanding the extent to which firefighters are exposed to a broad range of chemicals is especially critical in light of finding an increased risk of malignant mesothelioma, a disease that is mainly attributed to asbestos exposure.[57]

1.3 Chemical management in the United States

The chemical industry has produced trillions of pounds of chemicals, including flame retardant chemicals since World War II, with more than 80,000 registered chemicals that are currently in production.[58] Industry and modern society have benefitted greatly from chemicals. Despite this, little is known about the toxicity and safety of the numerous chemicals in circulation. Regulation surrounding safe chemical use in the United States has long been considered insufficient.[59–61] The Toxic Substances Control Act of 1976 (TSCA) oversees the safe use of chemicals in the United States and is the primary environmental law regulating chemicals in the United States. When first implemented, TSCA grandfathered in the approximately 60,000 existing chemicals at the time, including flame retardant chemicals, allowing them to remain in use without requiring evaluation of the potential health effects of these tens of thousands of chemicals.[61] Though TSCA was recently amended in 2016, it still does not require chemicals to be tested for safety before they are introduced to the market. Furthermore, the burden to prove that a chemical is unsafe lies with governmental agencies like the United States Environmental Protection Agency (US EPA)

rather than the chemical manufacturer. As a result of this safety loophole in TSCA regulation, very little is known about the toxicity of the 80,000 chemicals used worldwide. This has led to an interesting iterative process of cycling through chemicals when one is suspected to be harmful and is removed from the market for a certain application. Flame retardant chemicals are one such class of chemicals that have seen several iterations since their introduction to manufactured materials in the 1970s.

The US EPA has tried to address the data gaps in chemical safety research through their Chemical Safety and Sustainability program. This research plan proposes the sustainable development of safer chemicals[62] to consider the full effects of a chemical before it is released into the market. Furthermore, the EPA included the PBDE congener, BDE-209, on its Voluntary Children's Chemical Evaluation Program (VCCEP).[63] Though this research plan addresses flame retardant chemicals, it does not address all the chemicals that are currently registered under TSCA and currently in production.

1.4 Chemical alternatives assessments and life cycle assessments

The US EPA has used chemical alternatives assessments to identify safer alternatives for problematic flame retardants in printed circuit boards. Industries, like the textile and garment industry and the electronics industry, also use chemical alternatives assessments to "green" their manufacturing processes to improve occupational and environmental safety. Chemical alternatives assessments compare hazards among viable alternatives and ideally, include life cycle assessments (LCAs). Life cycle assessments (LCAs) are used to identify and potentially reduce a product's environmental and health impact at each stage in its life, from resource extraction to manufacture to distribution to use to disposal (i.e., from cradle to grave).[64] They can also be applied to chemical classes such as flame retardant chemicals. As a product or chemical runs through the course of its life, it generates inputs and outputs at each stage. These inputs and outputs can be captured quantitatively to compare the advantages and disadvantages at each life stage. The environmental impact at each life stage is separated into categories such as climate change, acidification, human toxicity, exposure, and risk. LCAs are used to recognize and solve problems throughout a value chain without shifting burden from one environmental impact to another environmental impact.[65]

For public health, the most relevant impact category evaluated within an LCA is human toxicity and exposure. In the current LCA framework, exposure assessments to determine human health impacts focus on outdoor emission sources and do not evaluate indoor consumer or occupational emissions and exposures.[66] Ignoring indoor consumer emissions and exposures could underestimate the environmental burden experienced by the general population, while overlooking occupational emissions and exposures could shift environmental burden from the general population to the working population.[67] Efforts to integrate occupational exposures have relied on inhalation measures as experienced by workers in metal degreasing, dry cleaning,[68] and the vehicle repair industry.[69] Inhalation is an important pathway for occupational exposures. However, occupational settings such as fire stations approximate residential settings where flame retardants are more likely to enter the body via ingestion.[70] Thus, pathways such as dermal contact and ingestion could also play a large role in exposing workers. Disregarding other pathways of exposure could underestimate occupational exposures.[68]

1.5 Research objectives and chapter overview

My research objectives are:

Chapter 2 – To describe the contamination of the legacy flame retardant, polybrominated diphenyl ethers, and the re-emerging organophosphate flame retardants in fire station dust across the United States.

Chapter 3 – To evaluate the potential health effects of the re-emerging organophosphate flame retardant, evaluating the association between maternal concentrations of flame retardant in urine and levels of sex hormones in male children at age 12.

Chapter 4 – To compare the risk of harm between two chemicals considered for a manufacturing processing step within the electronics industry and discuss the need to combine risk assessments with chemical alternatives assessments in selecting safer substitutions for chemicals of concern.

I summarize my research findings in Chapter 5, and discuss implications of my research findings and future research needs.

Chapter 2 – Organophosphate flame retardants in dust collected from United States fire stations[1]

2.1 Abstract

Firefighters are exposed to chemicals during fire events and we previously demonstrated that fire station dust has high levels of polybrominated diphenyl ethers (PBDEs). In conducting the Fire Station Dust Study, we sought to further characterize the chemicals to which firefighters could be exposed – measuring the emerging class of phosphorous-containing flame retardants (PFRs) in fire stations, for the first time, as well as PBDEs. Dust samples from 26 fire stations in five states were collected from vacuum-cleaner bags and analyzed for PFRs and PBDEs. PFR concentrations were found to be on the same order of magnitude as PBDE concentrations (maximum PFR: 218,000 ng/g; maximum PBDE: 351,000 ng/g). Median concentrations of tri-n-butyl phosphate (TNBP), tris (2-chloroisopropyl) phosphate (TCIPP), and tris(1,3-dichloroisopropyl)phosphate (TDCIPP) in dust from fire stations were higher than those previously reported in homes and other occupational settings around the world. Total PFR levels did not vary significantly among states. Levels of TDCIPP were higher in stations where vacuum cleaners were used to clean surfaces other than the floor. PBDE levels were comparable to those found in our previous study of 20 California fire stations and much higher than levels in California residences. PFR and PBDE levels in fire station dust are higher than in other occupational and residential settings, underscoring the need to identify and control sources of this contamination.

2.2 Introduction

Flame retardants have been used widely in United States consumer products such as furniture foam, plastic electronics casings, and even clothing since the 1970s with the intention of delaying the ignition of fire.[4] Concern over adverse health effects, persistence, and bioaccumulation has led to the phase-out of one class of flame retardants known as polybrominated diphenyl ethers (PBDEs)[4] and phosphorous-containing flame retardants (PFRs) have emerged as replacements in the commercial market.[25,71] The effects of PFRs on human health have not been well described, though animal research suggests these chemicals may act as endocrine disruptors.[26,27] The chlorinated PFRs tris(chloroethyl)phosphate (TCEP), tris (2-chloroisopropyl) phosphate (TCIPP), and tris(1,3-dichloroisopropyl)phosphate (TDCIPP) have been associated with carcinogenicity in animals;[23,28] rats fed TCEP for two years developed kidney tumors and rats fed TDCIPP for two years developed tumors of the kidney, liver, testis, and adrenal gland.[72] PFRs have been found in the indoor air[73,74] and dust[74,75] of multiple microenvironments,[23] including work environments; however, PFRs have not been previously measured in fire stations.

Firefighters experience a wide range of occupational health hazards, from ergonomic hazards[35–37] to post-traumatic stress[37–40] to overexertion.[35] They also may be at increased risk for leukemia,[52]

[1] This manuscript has been published: Shen B, Whitehead TP, Gill R, Dhaliwal J, Brown FR, Petreas M, Patton S, Hammond SK. Organophosphate flame retardants in dust collected from United States fire stations. *Environment International*. **2018**, *112*, 41-48.

testicular cancer,[53–55] prostate cancer,[54,55] multiple myeloma,[54] and malignant mesothelioma.[56] Firefighters are exposed to a wide range of chemicals including flame retardants[76,77] while they actively suppress fires[41–47] or check for hidden fires after completing fire suppression.[48–51] However, firefighters spend a considerable amount of on-shift downtime at their fire stations, where their exposures to chemicals have not been well characterized.

In 2010-2011, as part of the Firefighter Occupational Exposures (FOX) study, concentrations of PBDEs, novel brominated flame retardants, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls were measured in dust samples collected from the vacuum cleaner bags of 20 fire stations in Southern California.[32,78] The FOX study found elevated levels of BDE-209, in particular, when compared to other occupational and residential settings. Specifically, the FOX study found that median BDE-209 concentrations were 18-fold higher in dust from fire stations than in dust collected during the same time period from California residences and analyzed by the same methodologies.[32] This, along with the elevated PBDE concentrations in the blood of FOX participants,[33,34] indicates that California firefighters are exposed to higher levels of certain PBDEs than the general population.

In this follow-up study of 26 additional fire stations from five states, concentrations of PFRs were measured in fire station dust for the first time. The presence of high levels of PBDEs in dust from California homes has been reported in multiple studies,[25,79] likely as a result of California's unique flammability standards. Correspondingly, this study sought to evaluate whether California fire stations had uniquely high levels of PBDEs or if elevated PBDE levels were also present in fire stations located in other states.

2.3 Materials and Methods

2.3.1 Fire station recruitment. In 2015, the Fire Station Dust Study (FSDS) worked with the International Association of Fire Fighters (IAFF) to recruit five fire stations from each of five states (California, Minnesota, New Hampshire, New York, Texas). An additional pilot fire station from California was used to refine sampling protocols prior to launching the study.

2.3.2 Dust sampling. We collected bags from vacuum cleaners used for routine dust removal in the living quarters of 26 fire stations in 2015. We mailed sampling packets to each fire station and included: 1) a sampling protocol describing how to seal and ship the vacuum bag; 2) a re-sealable 36 cm x 61 cm x 0.2-mm thick polyethylene bag to contain the vacuum cleaner bag; 3) a questionnaire acquiring general fire station information and fire station cleaning practices; and 4) a preaddressed, prepaid envelope in which to mail the vacuum-cleaner bag to the Environmental Chemistry Laboratory at the California Department of Toxic Substances Control (DTSC) in Berkeley, California. We received a total of 26 vacuum-cleaner bags, including the vacuum-cleaner bag from the pilot fire station. Samples remained in the polyethylene bag at room temperature at DTSC until analysis.

2.3.3 Surveys. Fire station personnel completed a survey about the brand and model of their vacuum cleaner as well as the cleaning protocols they use for fire engines, fire stations, and turnout gear in an attempt to capture potential determinants of flame retardant concentrations.

2.3.4 Chemical analysis. Dust samples were sieved to remove fibers and debris larger than 150 μm. The extraction method was adapted from a previously described method.[80] Briefly, we weighed approximately 50 mg of the resulting fine-dust fraction, spiked it with a mixture of labeled internal standards (Supporting Information, Table S1) and extracted the analytes by sonication in a 3:1 hexane:acetone solution. The extracts were cleaned using Florisil column chromatography, then solvent-exchanged into isooctane and spiked with two labeled injection standards (Supporting Information, Table S1) yielding final extract volumes of 100 μL for the PBDE fraction and 1mL for the PFR fraction. We analyzed the samples in three sample batches: the first two batches contained nine dust samples and the third batch contained eight dust samples. Each sample batch also contained a duplicate, two method blanks, a laboratory control, and a standard reference material (NIST SRM No. 2585; Supporting Information, Table S2). We analyzed the extracts for five PFRs using electron impact ionization mode gas chromatography-tandem mass spectrometry.[81] We also analyzed 18 PBDEs via high-resolution gas chromatography-mass spectrometry operated in electron impact ionization mode, following the same analytical protocols we described in the FOX study for dust samples collected from Southern California fire stations[32] and reference California homes.[82] We calculated method reporting limits (MRLs) as three times the standard deviation of the method blank values for each analyte from three sample batches.

2.3.5 Statistical methods. Summary statistics and figures were generated using Microsoft Excel (Microsoft Office 2011 for Mac OS X). Statistical analyses were performed in R (R Core Team. 2016. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing). Pearson correlation coefficients were used to evaluate the relationships between analytes. To characterize the geographic variability of the flame retardants, we estimated within-state (σ^2_w) and between-state (σ^2_b) variance components and then calculated two descriptive ratios using the following equations:

(Eq. 1) Lambda, $\lambda = \frac{\sigma^2_w}{\sigma^2_b}$

(Eq. 2) Intraclass correlation coefficient, $\rho = \frac{\sigma^2_b}{\sigma^2_b + \sigma^2_w}$

We tested for differences in flame retardant levels by other explanatory factors (including age of building, turnout gear cleaning policies, turnout gear storage policies, and vacuum cleaner usage) using ANOVA. Chemical concentrations were log transformed prior to analysis. Significant associations were determined at $\alpha \leq 0.05$.

2.4 Results and Discussion

2.4.1 Characteristics of fire stations. A survey was returned by 25 of the 26 fire stations (6 of 6 from California, 5 of 5 from Minnesota, 5 of 5 from New Hampshire, 5 of 5 from New York, 4 of 5 from Texas). About half (56%) of the fire stations were built before 1970 and the rest (44%) were built after 1970. Most of the fire stations had turnout gear cleaning policies (80%) and designated areas for turnout gear storage (92%). In 68% of fire stations turnout gear was stored in the apparatus bay, in 4% in the living quarters, and in 12% in another space (16% of fire stations did not respond to this question). Turnout gear was stored in an enclosed area in 65% of the fire stations, but only 45% of the fire stations had ventilated storage areas. Turnout gear was explicitly banned from 92% of the fire stations' living quarters.

2.4.2 Concentrations of flame retardants in dust collected from FSDS fire stations. We detected each of the five PFR compounds in each of the dust samples with concentrations ranging from 177 ng/g to 218,000 ng/g (Table 1; Supporting Information, Table S3).

The highest measured PFRs were on the same order of magnitude as the highest measured PBDEs (maximum PFR, TDCIPP: 218,000 ng/g; maximum PBDE, BDE-209: 351,000 ng/g). TDCIPP and TPHP were the dominant PFR compounds in the dust samples; TDCIPP represented at least 50% of Σ_5 PFRs for eight dust samples and TPHP represented at least 50% of Σ_5 PFRs for six dust samples (Supporting Information, Figure S1). TDCIPP was the highest measured PFR in 15 of 26 samples, TPHP was the highest measured PFR in 10 dust samples, and TCIPP was the highest measured PFR in one fire station.

We detected each of the 18 PBDE congeners in each of the dust samples with concentrations ranging from 1.22 ng/g to 351,000 ng/g (Table 1; Supporting Information, Table S3). BDE-209 was the dominant congener found in most of the dust samples followed by BDE-47 and BDE-99; for 21 dust samples, BDE-209 concentrations represented at least 50% of Σ_{18} PBDEs (Supporting Information, Figure S2).

2.4.3 Differences in chemical levels within and between states. None of the PFR compounds measured had statistically significant differences among states (Table 2). For some of the flame retardants, the within-state variance estimate was very large making it impossible to observe potential between-state variance; the between-state variance estimate was zero in these instances (Figure 1).

Table 1. Summary of PFR and PBDE concentrations (ng/g) in 26 dust samples from 26 fire stations in the Fire Station Dust Study (FSDS) [2015], compared to median concentrations in dust samples collected from FOX fire stations [2010-2011; n=27][32] and California residences [2010; n=203] that were analyzed using the same protocols as FSDS samples.[82]

Flame retardant	Method reporting limit (MRL)	% of FSDS samples above MRL	FSDS minimum	FSDS median	FSDS mean	FSDS maximum	FOX median	CA residential median
PFRs								
TNBP	0	100	177	260	358	1,480	NM	NM
TCEP	0	100	178	1,040	1,320	4,660	NM	NM
TCIPP	323	100	499	3,880	5,040	37,400	NM	NM
TDCIPP	1,240	100	1,650	10,900	22,600	218,000	NM	NM
TPHP	0	100	1,150	10,800	14,100	85,400	NM	NM
PBDEs								
BDE-17	0.21	100	1.30	6.87	18.3	195	NM	NM
BDE-28	0.14	100	5.11	24.1	77.4	1,000	40.3	20
BDE-47	0.64	100	404	3,050	12,800	161,000	5,170	1,300
BDE-66	0.04	100	9.29	59.9	263	3,670	NM	NM
BDE-99	2.07	100	465	4,180	22,800	338,000	9,240	2,100
BDE-100	0.76	100	87.9	756	5,000	82,000	1,720	330
BDE-153	0.32	100	73.0	489	2,300	29,400	1,220	290
BDE-154	0.42	100	42.9	344	1,730	22,400	919	150
BDE-183	0.12	100	9.05	41.6	113	764	77.9	17
BDE-196	0.03	100	9.06	53.3	62.0	176	76.6	8.2
BDE-197	0.08	100	5.17	25.9	39.3	391	51.1	7.6
BDE-201	0.11	100	4.02	14.3	17.9	41.5	NM	NM
BDE-202	0.05	100	1.22	4.25	5.38	13.7	NM	NM
BDE-203	0.03	100	5.95	61.1	78.8	271	NM	NM
BDE-206	1.24	100	60.1	1,900	2,340	9,490	1,130	75
BDE-207	1.84	100	82.6	1,130	1,230	3,320	592	54
BDE-208	0.83	100	51.7	533	578	1,400	379	33
BDE-209	73.9	100	1,990	57,000	83,300	351,000	47,000	2,500

NM = not measured

Table 2. Estimated variance components and variance ratios from random effects model describing within-state and between-state variability.

	Variance components		Variance ratios	
Flame retardant	**Between state, σ^2_b**	**Within state, σ^2_w**	**Lambda[a], λ**	**Intraclass correlation coefficient[b], ρ**
PFRs				
TNBP	0	0.20	-	0
TCEP	0	0.62	-	0
TCIPP	0	0.69	-	0
TDCIPP	0.22	1.08	4.92	0.17
TPHP	0	0.83	-	0
PBDEs				
BDE-17	0.16	1.21	7.37	0.12
BDE-28	0.09	1.38	16.19	0.06
BDE-47	0.48	1.61	3.33	0.23
BDE-66	0.31	1.72	5.51	0.15
BDE-99	0.55	1.72	3.13	0.24
BDE-100	0.53	1.78	3.36	0.23
BDE-153	0.42	1.61	3.79	0.21
BDE-154	0.50	1.68	3.35	0.23
BDE-183	0	1.37	-	0
BDE-196*	0.27	0.50	1.84	0.35
BDE-197	0.09	0.77	8.31	0.11
BDE-201*	0.28	0.30	1.08	0.48
BDE-202*	0.35	0.25	0.71	0.59
BDE-203*	0.38	0.86	2.28	0.30
BDE-206*	0.82	1.04	1.27	0.44
BDE-207*	0.42	0.61	1.44	0.41
BDE-208*	0.35	0.46	1.29	0.44
BDE-209*	0.89	1.22	1.36	0.42

*Significance found at $p<0.05$; null hypothesis: chemical concentrations do not vary among states.

[a] Lambda, $\lambda = \frac{\sigma^2_w}{\sigma^2_b}$

[b] Intraclass correlation coefficient, $\rho = \frac{\sigma^2_b}{\sigma^2_b + \sigma^2_w}$

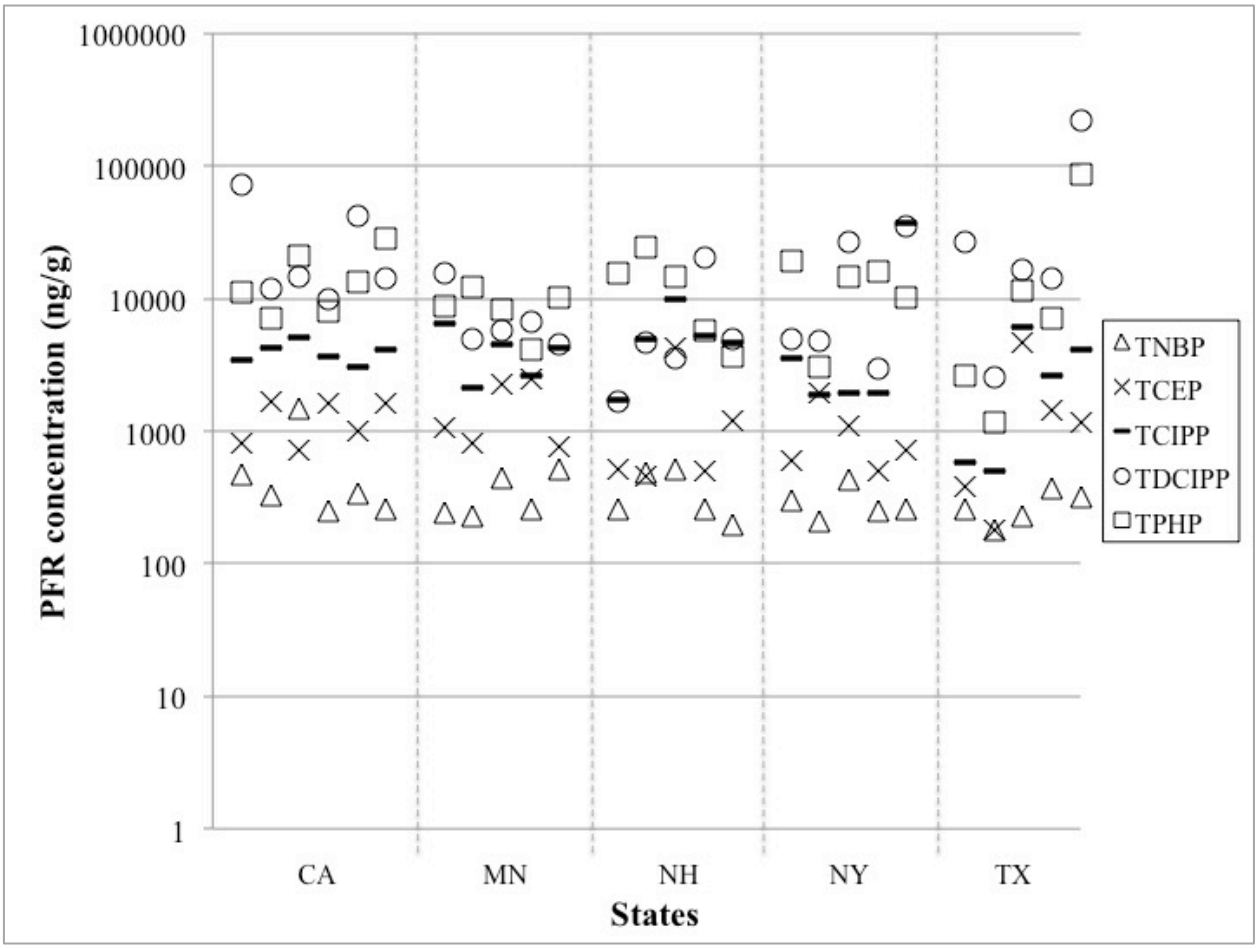

Figure 1. Concentrations (ng/g) of PFR compounds from each dust sample (n=26), clustered by state.

Dust from Texas had the highest concentrations of TDCIPP and TPHP, but also had the largest within-state variability for both PFRs (Figure 1, Supporting Information Table S4). Large within-state variance in PFR concentrations made it difficult to assess differences among states – with intra-class correlation coefficients (ICCs) of no more than 0.17 (TDCIPP, Table 2). Future studies with larger sample sizes and information on additional characteristics of fire station activities are required to further elucidate potential differences in PFR levels among the states.

PBDE concentrations also varied widely from different fire stations in the same state. Texas had the largest within-state variability for BDE-47 and BDE-99, and Minnesota had the largest within-state variability for BDE-209 (Figure 2, Table S4). When compared among states, concentrations of the major BDE congeners (BDE-47, -99, and -209) varied widely. Between-state variance accounted for 23% to 42% of total variance in levels of BDE-47, BDE-99, and BDE-209 (ICC range: 0.23 to 0.42, Table 2). Median levels for the higher brominated BDE congeners were significantly higher in California than in the other four states in the study (BDE-196, $p = 0.02$; BDE-201, $p = 0.003$; BDE-202, $p = 0.0003$; BDE-203, $p = 0.03$; BDE-206, $p =$

0.005; BDE-207, p = 0.008; BDE-208, p = 0.005; BDE-209, p = 0.007). Previous studies have reported elevated levels of the *lower* brominated BDEs in California house dust compared to other states. Lower-brominated BDEs are the primary constituents of PentaBDE, the commercial mixture that was used to treat furniture foam in order to achieve compliance with the State's unique furniture flammability standards.[79] In contrast, *higher* brominated BDEs are not typically found at exceptionally high levels in California house dust when compared to house dust levels from other states.[25,83] These higher-brominated BDEs comprised the other two commercial BDE mixtures, OctaBDE and DecaBDE, which were commonly used in electronics and plastic products.[84] In our study, whereas we did not find a significant difference in the *lower* brominated BDEs between the five states; we did observe elevated levels of the *higher* brominated BDEs in California. These findings suggest that California fire stations may have a source of elevated PBDE levels that are not associated with the State's unique furniture flammability standard, and that this contamination is perhaps originating from electronics.

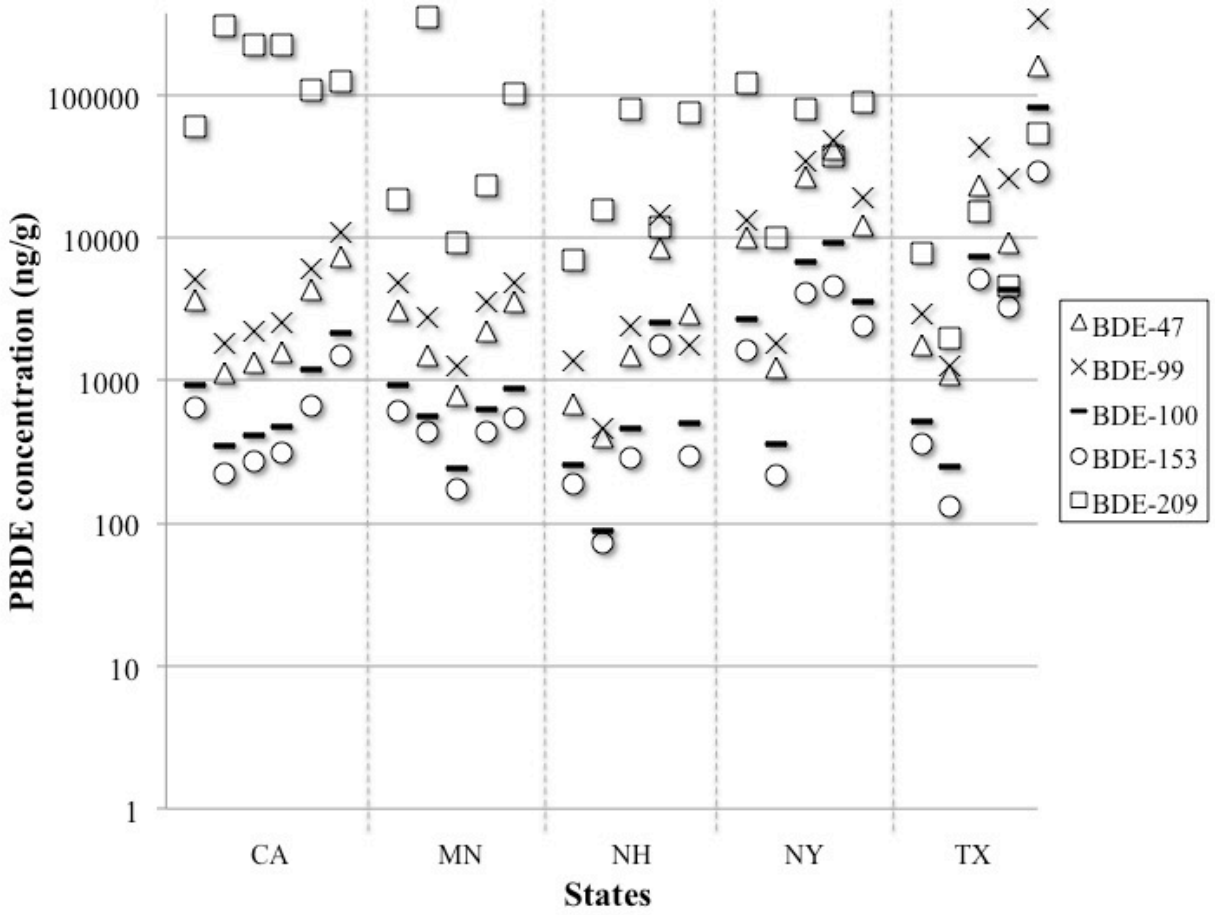

Figure 2. Concentrations (ng/g) of major PBDE congeners -47, -99, -100, -153, and -209 from each dust sample (n=26), clustered by state.

2.4.4 Differences in chemical levels by other explanatory factors. In ANOVA analysis comparing chemical concentrations by vacuum use, where the null hypothesis was that chemical concentrations do not vary by vacuum use, TDCIPP was the only chemical measured to show a significant difference ($p = 0.03$) in levels between fire stations that used vacuum cleaners on floor surfaces only (median TDCIPP: 5,800 ng/g) and fire stations that used vacuum cleaners on surfaces other than the floor (median TDCIPP: 27,800 ng/g). TDCIPP and TCEP are both commonly used as flame retardants in textiles,[25] though we did not observe a corresponding significant differences in TCEP levels by cleaning practices. There were no significant relationships between flame retardant concentrations and any other explanatory factors.

2.4.5 Correlation between analytes. Levels of the two dominant PFRs - TDCIPP and TPHP - were not significantly correlated, suggesting that they may originate from different sources. Indeed, though both are used in polyurethane foams, TPHP is also used as a flame retardant plasticizer and as a lubricant.[85] Additionally, among the PFRs measured in this study, only TPHP is a major component of Firemaster 550, a flame retardant mixture used in furniture foam as a replacement for the phased-out PentaBDE mixture.[86] Within the PFR analytes, only TNBP (used as a plasticizer and lubricant) and TCIPP (used in polyurethane foam) showed significant correlations ($r = 0.43$) with TPHP (used as plasticizer and lubricant, and in polyurethane foam); TCEP and TCIPP (both used in polyurethane foams) were also significantly correlated ($r = 0.43$). TCIPP was also significantly correlated with the higher brominated PBDEs (r range: 0.39 – 0.44). TDCIPP showed significant correlations with the lower brominated PBDEs (r range: 0.42 – 0.59); both TDCIPP and lower brominated BDEs that make up PentaBDE are used in polyurethane foams. TPHP had significant correlations with all the brominated flame retardants, excepting BDE-197 (Supporting Information, Table S5). BDE congeners were highly correlated within two groups; Pearson correlation coefficients ranged from 0.66 to 0.99 among the lower brominated PBDEs (BDE-17 to BDE-183), and from 0.71 to 0.99 among the higher brominated PBDEs (BDE-196 to BDE-209).

2.4.6 Calculating exposure doses. This study observed elevated levels of PFRs and PBDEs in fire stations. If one assumes that an 80 kg person ingests 30 mg of dust a day,[87] then the maximum PBDE concentrations found in our study -- 338,00 ng/g for BDE-99 and 351,000 ng/g for BDE-209 -- correspond to doses of 1.27×10^{-4} mg/kg-day for BDE-99 and 1.32×10^{-4} mg/kg-day for BDE-209. The United States Environmental Protection Agency (U.S. EPA) suggests a maximum oral reference dose of 1×10^{-4} mg/kg-day for BDE-99 and 7×10^{-3} mg/kg-day for BDE-209 (the U.S. EPA does not provide oral reference doses for PFRs).[88] Via the unintentional ingestion of settled dust, firefighters at certain fire stations may be exposed to levels of BDE-99 over the U.S. EPA's suggested levels. Firefighter *total* exposure doses could be even higher if all routes of exposure (dermal, diet, inhalation) were considered. Moreover, the previous FOX study observed elevated PBDE levels in firefighter serum compared to a reference population in California,[34] suggesting biological uptake within this occupation.

2.4.7 Concentrations in fire stations vs. other settings. Median TNBP, TDCIPP, and TPHP levels in fire station dust were higher than those previously reported in occupational and residential settings, including a study that measured PFRs in 2011 in California house dust (Figure 3).[25]

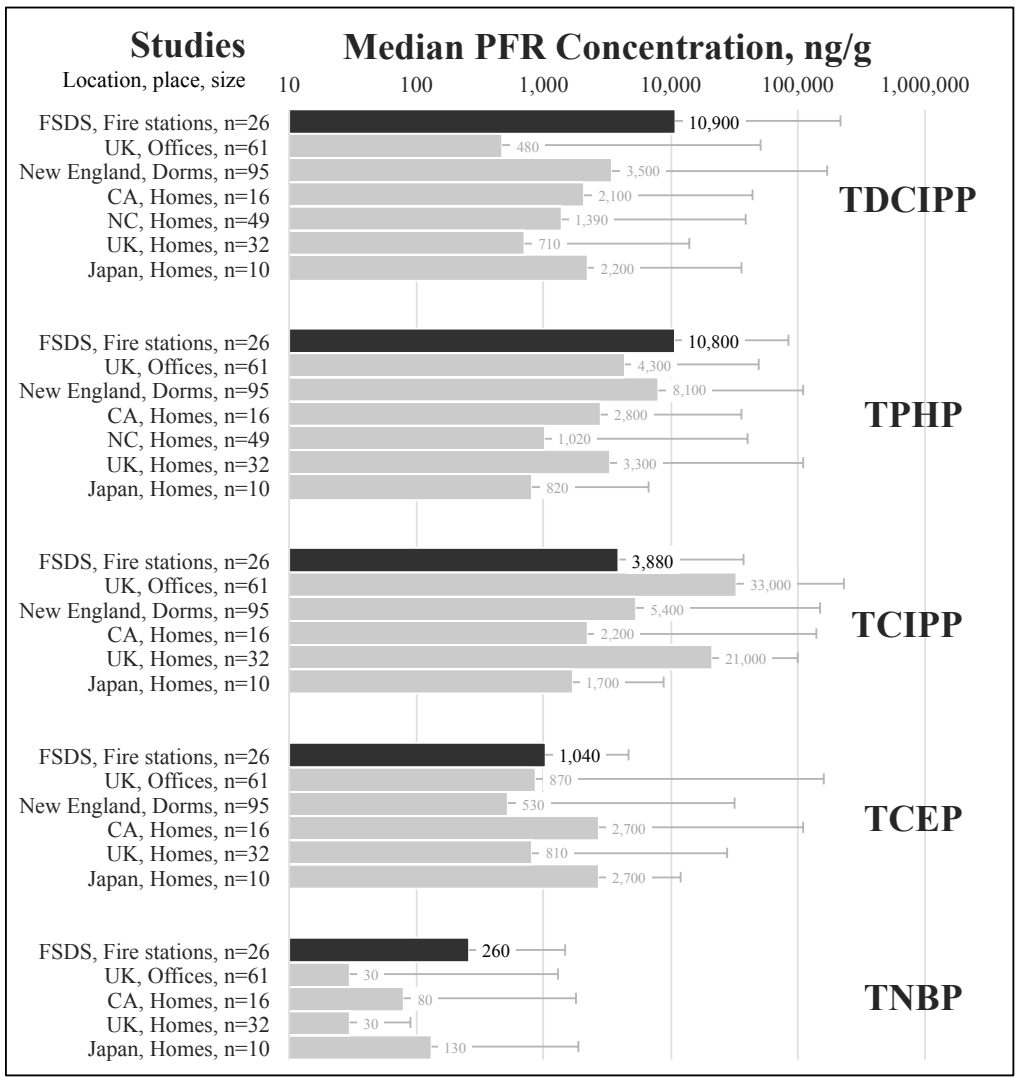

Figure 3. Median concentrations of PFRs in dust (ng/g, shown on a logarithmic scale) with positive error bars representing maxima from the Fire Station Dust Study (collected in 2015), other occupational settings, and residential settings. Data for UK offices and homes (collected 2011-2012) from Brommer and Harrad,[89] for New England dorms (collected in 2015) from Dodson et al.,[90] for CA homes (collected in 2011) from Dodson et al.,[25] for NC homes (collected in 2012, geometric mean, only TDCIPP and TPHP reported) from Hoffman et al.,[91] and for Japanese homes (collected 2009-2010) from Mizouchi et al.[92]

We also corroborated our findings from the FOX study, showing again that median dust concentrations of all BDE congeners were substantially higher in the FSDS California fire stations than in the reference population of California homes (sampled in 2010, and analyzed using the same analytical protocols). Specifically, the very high levels of BDE-209 observed in dust from California fire stations in the FOX study were once again evident in the California fire stations of the FSDS study (Supporting Information, Figure S3). In measuring dust-PBDE levels in fire stations from other states for the first time, we found median concentrations of the major

BDE congeners to be higher than other occupational settings and residential settings, including in the reference population of California homes (Supporting Information, Figure S3). Overall, median concentrations of the major BDE congeners were higher in this study than those from other occupational and residential settings; only our previous FOX study has reported higher median concentrations of BDEs-47, -99, -100, and -153 in indoor dust.

Given that fire stations have higher levels of PFRs and PBDEs compared to other occupational and residential settings, future research should focus on implicating flame retardant sources that are unique to fire stations such as specialized firefighting equipment (e.g., turnout gear and fire engines), and contamination that is tracked back from fire-incident sites. Indeed, some studies have observed contamination of turnout gear surfaces by PFRs[76] and PBDEs[76,93,94] after fire incidents, and some station gear has been shown to purposely contain the mineral flame retardant, antimony.[95] These and other studies have demonstrated the potential for dermal absorption of flame retardants by firefighters and the benefit of turnout gear cleaning for reducing PBDE serum levels.[34] As such, we propose that flame retardants may be tracked from fire responses back to fire stations via contaminated turnout gear, resulting in the contamination of fire station dust. Chemical track-back such as this has been observed in agricultural communities with pesticides.[96–98] Moreover, the previous FOX study found a positive relationship between PAH levels in fire station dust and the number of fire and hazardous material incidents, suggesting that firefighters track-back PAHs on contaminated gear and equipment from fire incidents to the fire station.[32] Although we were unable to obtain information regarding the number of responses to fire incidents per station for this study, future studies should include this information along with turnout gear wipe and fire station dust measurements to further elucidate potential track-back of flame retardants from fire sites to fire stations. Future studies should also include analyses examining the relationship between flame retardant levels in dust and consumer products, such as furniture and electronics, which are present in the fire stations. The quantities of specific consumer products within a household have been shown to be positively correlated with PBDE levels in house dust (e.g., furniture associated with PentaBDE and electronics associated with DecaBDE).[99] Given that consumer products are often the source of flame retardant contamination in residential homes,[4,79,99] the amount of consumer products in fire stations such as beds, couches, recliners, televisions, and computers could potentially explain the differences in flame retardant levels between fire stations and residential homes. Future research should include detailed surveys observing the types and number of consumer products, and amount of foot traffic within fire stations to compare to households for evaluation of flame retardant level differences. Additionally, information on the type of flammability standard that furniture in each fire station follows (e.g., TB117-2013; TB133; or other) may elucidate observed differences.[90] Such research would inform intervention practices to reduce flame retardant levels in fire stations and potentially reduce the exposure to flame retardants experienced by firefighters.

2.4.8 Limitations. We sampled dust collected from vacuum cleaners used for everyday cleaning at each fire station. The main advantages to this method are integration of chemical levels over space and time, convenience, and cost efficiency. The main limitation to this method is that vacuum cleaners and vacuum cleaning practices may differ from one fire station to the next, and introduce variability in chemical levels. Furthermore, we could not eliminate the possibility that the vacuum cleaners were made of materials containing either PFRs or PBDEs, potentially

causing us to overestimate PFR and PBDE levels in the fire station dust. However, the vacuum cleaners were commercially-available residential models which are commonly used in California homes,[82] one of the comparison populations used in this analysis. In spite of its limitations, vacuum-bag dust remains a useful medium for measuring indoor chemical contamination because indoor dust acts as a reservoir for semivolatile and nonvolatile environmental contaminants.

Despite a limited number of samples, we were able to observe statistically significant differences in PBDE concentrations among states. Specifically, BDEs 196, 201, 202, 203, 206, 207, 208, and 209 were higher in California fire stations than in fire stations from the other four states. For future studies, a larger sample size may assist in more rigorous statistical analyses to identify potential differences among states in PFR levels and explain differences in PBDE levels by state more conclusively.

2.5 Conclusions

Our findings from this study, as well as the previous FOX study, indicate that fire stations are contaminated with higher levels of flame retardants than residences and other occupational settings; thus, firefighters may be potentially exposed to higher levels of flame retardants than the general population. This follow-up study confirmed that flame retardant levels were elevated in fire stations from multiple states in addition to California. Future studies should focus on identifying the sources of flame retardants that are unique to fire stations such as contaminated gear and equipment, chemical track-back from fire incidents, or specific types of furnishings.

2.6 Acknowledgements

We thank all the firefighters and staff of the fire stations who participated in this study and generously provided time and cooperation. We also thank Neil Thayamballi for assisting in laboratory preparation. This work was supported by the International Association of Firefighters. Its contents do not necessarily represent the official views of the California Department of Toxic Substances Control.

2.7 Supporting Information

Table S1. PFRs and PBDEs measured and their internal and injection standards used during chemical analysis.

Chemical	Internal Standard[a]	Injection Standard[b]
PFRs		
TNBP	dTNBP	dTPP
TCEP	dTCEP	dTPP
TCIPP	dTCIPP	dTPP
TDCIPP	dTDCIPP	dTPP
TPHP	dTPHP	dTPP
PBDEs		
BDE-17	13C-PBDE-28	13C-PCB-209
BDE-28	13C-PBDE-28	13C-PCB-209
BDE-47	13C-PBDE-47	13C-PCB-209
BDE-66	13C-PBDE-47	13C-PCB-209
BDE-99	13C-PBDE-99	13C-PCB-209
BDE-100	13C-PBDE-99	13C-PCB-209
BDE-153	13C-PBDE-153	13C-PCB-209
BDE-154	13C-PBDE-154	13C-PCB-209
BDE-183	13C-PBDE-183	13C-PCB-209
BDE-196	13C-PBDE-197	13C-PCB-209
BDE-197	13C-PBDE-197	13C-PCB-209
BDE-201	13C-PBDE-197	13C-PCB-209
BDE-202	13C-PBDE-197	13C-PCB-209
BDE-203	13C-PBDE-197	13C-PCB-209
BDE-206	13C-PBDE-207	13C-PCB-209
BDE-207	13C-PBDE-207	13C-PCB-209
BDE-208	13C-PBDE-207	13C-PCB-209
BDE-209	13C-PBDE-209	13C-PCB-209

[a] All internal standards supplied by Wellington Laboratory Inc., Guelph, ON, Canada, except for 13C-PBDE-209 and dTCIPP (both supplied by Cambridge Isotope Laboratories, Inc., Andover, MA, USA)

[b] 13C-PCB-209 supplied by Wellington Laboratory Inc., Guelph, ON, Canada; dTPP supplied by Cambridge Isotope Laboratories, Inc., Andover, MA, USA

Table S2. QA/QC with SRM 2585 data.

Chemical	Average measured concentration in NIST replicates[a] (ng/g)	Coefficient of variation in NIST replicates (%)[a]	Certified NIST concentration (ng/g)	Percent error (%)
PBDEs				
BDE-17	13.0	29.1	11.5	12.9
BDE-28	52.0	4.53	46.9	10.9
BDE-47	633	4.14	497	27.3
BDE-99	992	0.970	892	11.2
BDE-100	168	6.06	145	15.5
BDE-153	144	0.448	119	21.3
BDE-154	87.0	2.29	83.5	4.13
BDE-183	51.4	1.93	43.0	19.5
BDE-203	34.3	1.21	36.7	6.42
BDE-206	245	7.70	271	9.65
BDE-209	4555	8.81	2510	81.5

[a] Average and coefficient of variation in 3 NIST replicates for PBDEs.

Table S3. Concentrations (ng/g) of each PBDE congener and PFR compound measured from each fire station by state.

Sample		*BDE congeners*																		*PFR compounds*				
by state		**17**	**28**	**47**	**66**	**99**	**100**	**153**	**154**	**183**	**196**	**197**	**201**	**202**	**203**	**206**	**207**	**208**	**209**	**TNBP**	**TCEP**	**TCIPP**	**TDCIPP**	**TPHP**
CA	**1**	8.68	36.3	3,690	72.4	5,130	944	652	451	39.0	69.6	30.1	25.2	8.23	69.0	2,340	1,390	774	60,200	477	814	3490	*71,400	11,300
	2	4.38	13.0	1,130	20.1	1,820	353	223	167	34.8	176	53.3	41.5	13.7	236	8,340	3,300	1,400	306,000	325	1,690	4,300	12,000	7,020
	3	3.46	11.4	1,360	25.4	2,200	409	269	200	42.1	132	42.9	34.1	12.0	158	5,610	2,210	1,000	223,000	1,480	715	5,160	14,800	20,700
	4	3.71	13.3	1,590	28.5	2,580	469	310	220	41.1	99.2	41.9	26.5	8.08	149	4,840	2,490	1,080	223,000	252	1,640	3,640	9,900	7,960
	5	10.3	38.4	4,400	117	6,030	1,190	669	491	45.5	115	37.3	35.7	12.2	104	2,740	1,540	800	108,000	334	1,000	3,030	41,800	13,500
	6	14.4	51.0	7,480	138	11,000	2,180	1,480	1,100	56.2	86.8	35.5	30.0	9.29	109	3,700	2,120	1,010	126,000	255	1,600	4,140	14,000	28,200
MN	**1**	6.46	26.0	3,140	58.5	4,820	925	609	423	32.3	28.5	20.3	12.9	3.68	27.9	639	599	339	18,700	243	1,080	6,510	15,300	8,860
	2	2.98	11.3	1,490	27.4	2,750	565	432	303	28.9	86.7	30.6	14.6	4.31	183	9,490	3,320	1,320	351,000	227	821	2,100	4,890	12,000
	3	1.95	7.03	797	14.9	1,280	241	175	116	9.62	15.2	6.83	5.37	1.66	13.2	351	283	164	9,250	441	2,240	4,470	5,680	8,160
	4	5.89	20.2	2,250	41.6	3,530	633	433	308	21.9	23.2	10.8	7.57	2.23	21.3	701	522	304	23,100	259	2,500	2,610	6,710	4,170
	5	8.25	31.9	3,620	61.4	4,900	879	545	380	28.7	61.2	24.2	18.2	5.40	60.5	2,810	1,620	853	104,000	509	769	4,290	4,500	10,200
NH	**1**	1.30	5.11	691	20.2	1,400	259	186	139	22.8	18.8	12.2	7.51	2.21	17.4	264	295	172	7,000	256	515	1,740	1,650	15,600
	2	2.43	8.51	404	9.29	465	87.9	73.0	42.9	64.8	22.7	27.5	6.88	1.91	22.0	615	413	227	15,800	492	462	4,980	4,710	*24,500
	3	3.65	13.5	1,480	37.2	2,400	464	289	207	17.7	53.1	21.8	14.0	4.20	98.7	2,440	1,510	663	81,000	518	4,200	9,960	3,590	14,400
	4	10.4	44.9	8,460	177	14,500	2,530	1,780	1,360	66.7	16.9	8.25	6.41	1.94	15.4	350	310	175	12,000	255	506	5,170	*20,500	5,810
	5	18.2	62.7	2,960	82.4	1,760	503	295	138	744	166	391	38.7	5.13	271	2,070	1,750	724	75,700	197	1,190	4,660	5,010	3,630
NY	**1**	19.5	61.8	10,100	172	13,400	2,670	1,640	1,210	67.8	94.0	37.3	27.4	8.36	130	3,830	2,190	974	122,000	299	590	3,540	4,870	18,900
	2	3.92	10.3	1,240	21.3	1,840	361	219	164	13.2	24.2	11.8	8.78	2.57	19.5	428	351	200	10,200	208	1,930	1,870	4,790	3,080
	3	33.5	131	26,700	465	34,100	6,820	4,110	3,200	164	90.7	46.5	28.8	9.08	108	2,920	1,630	751	80,700	429	1,090	1,960	26,400	14,600
	4	54.4	191	41,900	649	47,800	9,240	4,630	3,700	133	32.1	16.3	12.1	3.54	35.3	1,160	779	395	37,400	251	498	1,930	2,980	16,200
	5	17.2	56.8	12,100	209	18,900	3,570	2,410	1,830	88.2	53.5	27.5	20.5	6.20	73.4	2,430	1,300	593	88,000	259	711	37,400	35,000	10,100
TX	**1**	3.49	11.0	1,760	25.7	2,900	514	360	247	12.3	16.2	6.30	5.80	1.72	12.2	211	285	170	7,900	261	385	585	26,900	2,600
	2	2.14	9.23	1,090	19.5	1,270	252	130	97.6	9.05	9.06	5.17	4.02	1.25	5.95	60.1	82.6	51.7	1,990	177	178	499	2,520	1,150
	3	33.3	118	23,200	484	43,000	7,490	5,080	3,740	281	52.1	46.3	12.8	3.84	40.0	517	470	296	15,200	227	4,660	6,070	16,700	11,500
	4	7.28	22.2	9,260	185	25,900	4,390	3,260	2,320	109	12.4	6.21	4.33	1.22	9.61	171	200	113	4,650	367	1,430	2,650	14,200	7,100
	5	195	1,000	161,000	3,670	338,000	82,000	29,400	22,400	764	57.0	24.3	16.7	5.79	61.8	1,730	952	472	53,800	322	1,180	4,120	*218,000	85,400

*Concentrations measured were higher than the highest calibration point concentration and are estimates

Table S4. Coefficients of variation (%) of PFRs and major BDE congeners within each state.

		CA	MN	NH	NY	TX
PFRs	**TNBP**	91.6	38.6	43.5	29.2	27.9
	TCEP	36.0	55.7	117	60.6	115
	TCIPP	18.8	43.6	55.7	168	85.5
	TDCIPP	90.1	60.7	107	100	164
	TPHP	55.5	33.7	65.4	49.2	167
PBDEs	**47**	75.2	51.3	118	86.9	175
	99	72.9	43.9	143	77.5	175
	100	75.7	42.5	130	77.4	187
	153	78.8	37.7	135	69.4	161
	209	52.4	143	96.0	65.0	128

Table S5. Pearson correlation coefficients between dust concentrations of chemicals.

		PBDEs																	PFRs				
		17	*28*	*47*	*66*	*99*	*100*	*153*	*154*	*183*	*196*	*197*	*201*	*202*	*203*	*206*	*207*	*208*	*209*	*TNBP*	*TCEP*	*TCIPP*	*TDCIPP*	*TPHP*
PBDEs	*17*	1.00	0.99	0.96	0.96	0.90	0.92	0.90	0.88	0.82	0.33	0.35	0.37	0.36	0.29	0.25	0.27	0.28	0.24	-0.13	0.15	0.24	0.55	0.47
	28		1.00	0.96	0.96	0.90	0.92	0.90	0.88	0.81	0.31	0.33	0.35	0.34	0.27	0.24	0.25	0.26	0.22	-0.12	0.10	0.23	0.56	0.49
	47			1.00	0.99	0.98	0.99	0.98	0.98	0.73	0.18	0.14	0.22	0.25	0.14	0.13	0.14	0.15	0.13	-0.14	0.09	0.18	0.56	0.44
	66				1.00	0.97	0.98	0.97	0.97	0.77	0.19	0.18	0.24	0.25	0.16	0.13	0.14	0.15	0.12	-0.13	0.12	0.21	0.56	0.48
	99					1.00	0.99	0.99	0.99	0.66	0.11	0.03	0.15	0.20	0.08	0.10	0.10	0.11	0.09	-0.10	0.13	0.18	0.59	0.47
	100						1.00	0.99	0.99	0.70	0.14	0.08	0.18	0.22	0.11	0.12	0.12	0.13	0.11	-0.12	0.13	0.18	0.59	0.48
	153							1.00	0.99	0.69	0.13	0.07	0.16	0.21	0.10	0.12	0.12	0.13	0.11	-0.11	0.15	0.21	0.59	0.48
	154								1.00	0.66	0.12	0.03	0.15	0.21	0.09	0.12	0.12	0.13	0.10	-0.10	0.14	0.19	0.58	0.48
	183									1.00	0.41	0.60	0.40	0.31	0.39	0.26	0.28	0.27	0.25	-0.07	0.14	0.33	0.42	0.47
	196										1.00	0.88	0.97	0.94	0.98	0.92	0.94	0.94	0.92	0.25	0.28	0.37	0.25	0.41
	197											1.00	0.85	0.72	0.87	0.71	0.75	0.75	0.71	0.09	0.25	0.40	0.12	0.30
	201												1.00	0.97	0.94	0.88	0.91	0.91	0.88	0.24	0.22	0.39	0.31	0.41
	202													1.00	0.89	0.89	0.90	0.91	0.89	0.32	0.20	0.37	0.38	0.48
	203														1.00	0.95	0.97	0.96	0.95	0.23	0.28	0.41	0.18	0.42
	206															1.00	0.99	0.99	0.99	0.33	0.26	0.44	0.21	0.51
	207																1.00	0.99	0.99	0.28	0.27	0.42	0.20	0.48
	208																	1.00	0.98	0.29	0.28	0.42	0.22	0.49
	209																		1.00	0.31	0.23	0.42	0.20	0.47
PFRs	*TNBP*																			1.00	0.06	0.26	0.16	0.43
	TCEP																				1.00	0.43	0.11	0.17
	TCIPP																					1.00	0.24	0.43
	TDCIPP																						1.00	0.35
	TPHP																							1.00

Red indicates Pearson correlation coefficient differed significantly from zero, p-value < 0.05.

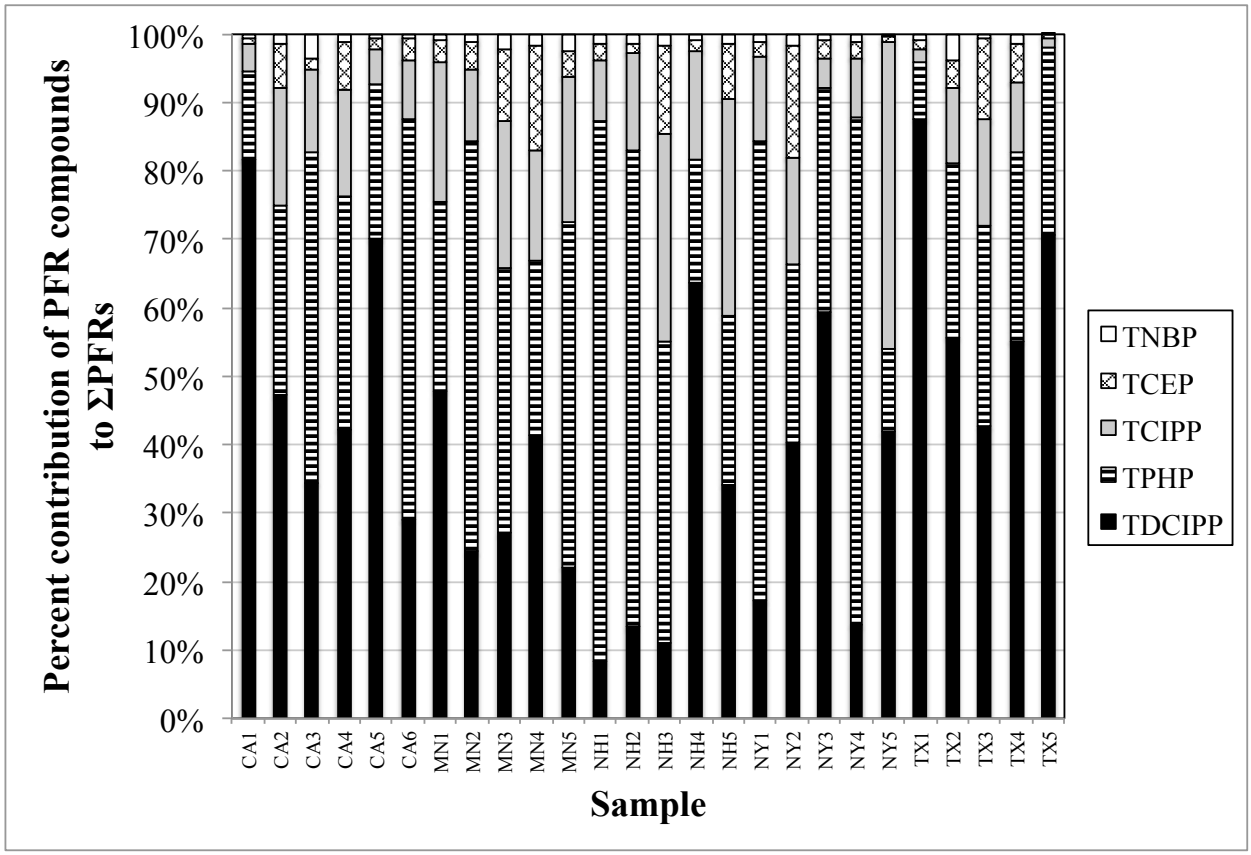

Figure S1. Contribution of each PFR compound measured from each dust sample (n=26), shown as percentage of ΣPFRs.

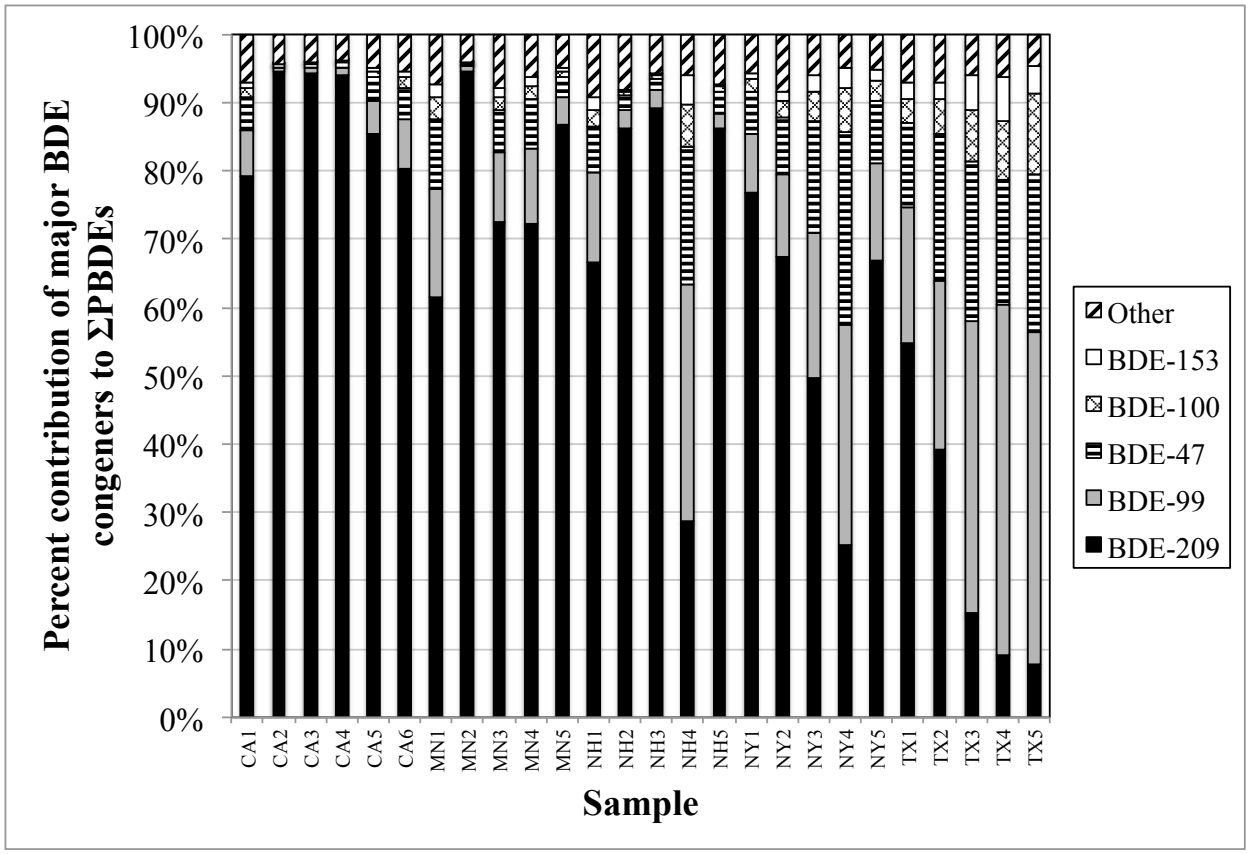

Figure S2. Contribution of the major PBDE congeners -47, -99, -100, -153, and -209 measured from each dust sample (n=26), shown as percentage of ΣPBDEs.

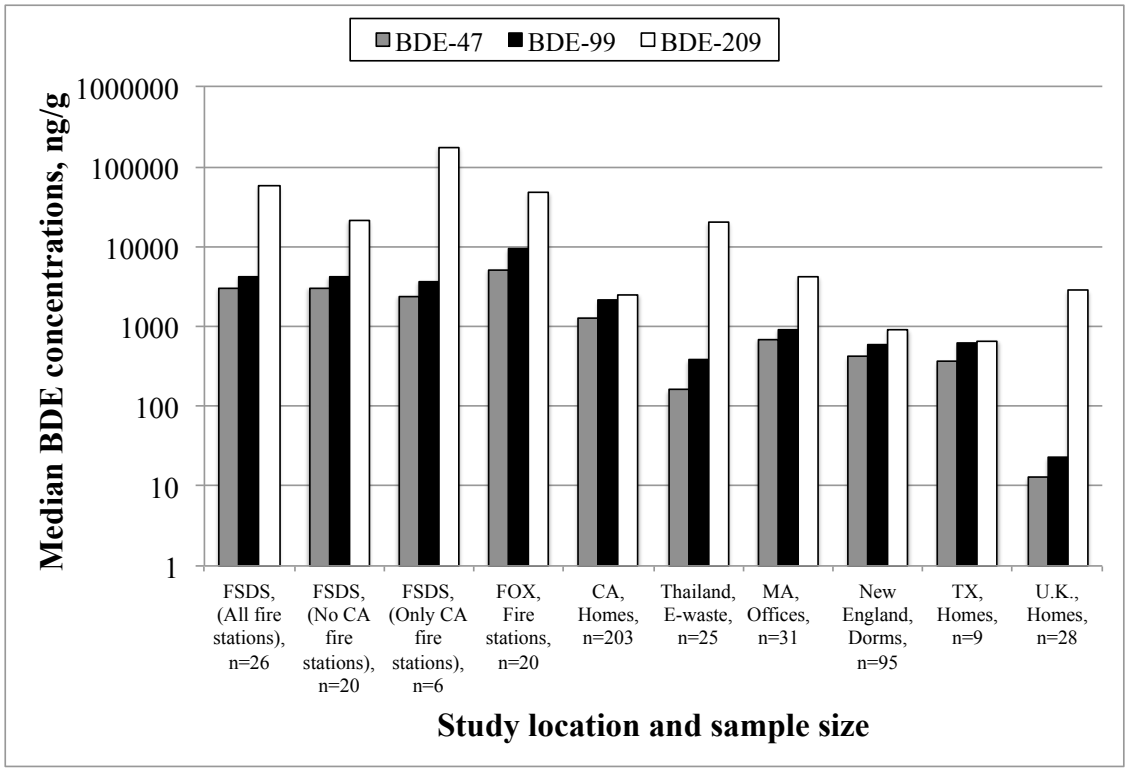

Figure S3. Median concentrations of major BDE congeners in dust (ng/g) from the Fire Station Dust Study, the FOX study, other occupational settings, and residential settings. Data from the Fire Station Dust Study (collected in 2015), the FOX study (collected in 2010-2011),[32] and the CA homes (collected in 2010)[82] were analyzed using the same analytical methods by the same laboratory. Data for Thailand e-waste recycling facility (collected 2007-2008) from Muenhor et al.,[29] for MA offices (collected in 2009, geometric mean) from Watkins et al.,[62] for New England dorms (collected in 2015) from Dodson et al.,[90] for TX homes (collection date unknown) from Schecter et al.,[19] and for UK homes (collected in 2006) from Harrad et al.[20]

Chapter 3 – In utero exposure to organophosphate flame retardants and sex hormones in male children at age 12[2]

3.1 Abstract

Organophosphate flame retardants (PFRs) have replaced polybrominated diphenyl ethers (PBDEs) as current-use flame retardants in some consumer products, but PFR human health effects are not well described. In this study, the first to examine PFR exposures in utero and their potential effects on sex hormone levels in adolescent boys, we used multivariate regressions to assess the relationship between four PFRs in prenatal maternal urine and follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone in a cohort of 12-year old male children residing in California's Salinas Valley. In adjusted models, we did not find any significant associations between PFR exposure and the hormone levels. However, we did see a marginal association between diphenyl phosphate (DPHP) and FSH indicating a 102.3% increase in FSH levels with every 10-fold increase in DPHP (95% CI: -12.1% to 370.1%) in maternal urine. We also observed a marginal association between bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and testosterone indicating a 62.0% increase in testosterone levels with every 10-fold increase in BDCIPP (95% CI: -7.6% to 184.2%). Although we did not observe any statistically significant associations, the trends that we did see indicate more research is needed to fully understand the impacts of PFR exposure on sex hormones.

3.2 Introduction

Flame retardants have been widely used in the United States since the 1970s[4] in consumer products such as furniture foam, electronics, plastics, and textiles. Current-use organophosphate flame retardants (PFRs) replaced many uses of polybrominated diphenyl ethers (PBDEs) in consumer products[25,71] after the phase-out of PBDEs because of increasing concern over their persistence, bioaccumulation, and toxicity.[4] PFRs are commonly found in the air and dust of indoor environments[23,100,101] such as offices,[73] fire stations,[102] daycare centers,[74] and homes.[25,75,92] They are also found in ecosystems such as surface waters,[103] seawater,[104,105] sediments,[106,107] and biota.[106]

Exposure to PBDEs, no longer in use, have been associated with endocrine effects on female menstruation and fecundability,[7,8] and hormone disruption.[9,14,108] PBDEs have also been associated with effects on reproductive hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone.[9,109,110]

The chlorinated PFRs tris(2-chloroethyl)phosphate (TCEP) and tris(1,3-dichloroisopropyl)phosphate (TDCIPP) are currently listed as known carcinogens in the state of California,[28] but few studies evaluate the effects of PFRs on human health and none have studied endocrine effects in children. Toxicological studies suggest these chemicals may have many biological effects, including effects on endocrine systems.[26,111–114] Animal research has also associated PFRs with adverse neurodevelopmental, reproductive, metabolic, and endocrine

[2] This is a manuscript in preparation for publication with the following co-authors: Kim G. Harley, Asa Bradman, and S. Katharine Hammond.

outcomes.[113,115,116] Triphenyl phosphate (TPHP) in particular has been linked with endocrine effects[114] through induction of estrogenic activity;[111,112] in vitro studies have shown agonistic activity on estrogen receptors by TPHP[114] and male mice fed TPHP showed decreased testicular testosterone.[27] Human studies characterizing the association between PFRs and FSH, LH, and testosterone are even scarcer, with one study to date that evaluated PFR associations between concentrations in house dust and hormone levels and semen quality in *adult* males,[117] but no such study exists for male children.

In this study, we evaluate the association between prenatal PFR exposure, assessed based on maternal urinary concentrations of PFR metabolites, and hormone levels of FSH, LH, and testosterone in 12-year boys from a birth cohort from California's Salinas Valley.

3.3 Methods

3.3.1 Study participants. This study uses data from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study examining environmental exposures and their health impacts on mothers and children residing in California's Salinas Valley, an agricultural community. Details on study recruitment and data collection are described elsewhere.[118,119] Briefly, 601 pregnant women were recruited at prenatal clinics serving the low-income predominantly Latino population from October 1999 to October 2000, 526 women remained in the study through the birth of their infants, 263 of whom were boys. 163 boys were followed through the age of 12. Of the 163 boys assessed at age 12, 112 provided blood for hormone analysis and 87 of these had information on prenatal PFR concentrations.

3.3.2 PFR measurements. PFRs were measured in urine collected during the mother's second prenatal study visit (mean gestational age: 26.9 weeks; standard deviation: 2.5 weeks). Urine samples were stored at -80°C in the CHAMACOS biorepository until transferred on dry ice to Duke University for analysis. Four PFR metabolites were measured in urine: TPHP metabolite diphenyl phosphate (DPHP), TDCIPP metabolite bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), isopropylphenol diphenyl phosphate metabolite isopropylphenol phenyl phosphate (ipDPP), and tert-butylphenyl diphenyl phosphate metabolite tert-butylphenyl phenyl phosphate (tbutylDPP), using negative electrospray ionization liquid chromatography-tandem mass spectrometry.[120,121] PFR concentrations below the method detection limit (MDL) were imputed at random based on a log-normal probability distribution with the cutoff at the limit of detection (LOD). Results were standardized by specific gravity.[120]

3.3.3 Hormone measurements. LH, FSH, and T levels were measured from serum samples collected from the male children during their 12-year visit. LH and FSH levels were analyzed by electrochemiluminescent assay.[109] After nonpolar solvent extraction, T levels were determined by liquid chromatography mass spectrometry.[109] All hormone analyses were performed at Esoterix Laboratory Services (Calabasas Hills, CA).

3.3.4 Statistical methods. Both exposure (PFRs) and outcome (hormone) variables were treated as continuous variables in multivariate regressions. PFR and hormone distributions were both right-skewed so were $\log_{10}$-transformed for statistical analysis. Each hormone was evaluated

separately with each of the four PFRs. We considered the following covariates for our model *a priori*: maternal education, maternal pre-pregnancy BMI, family poverty status at age 12, and child's age at the time of his hormone assessment. Ultimately, because of our limited sample size, we chose to include only maternal pre-pregnancy BMI and child's age at the time of his hormone assessment in our model. In sensitivity analyses, Tanner stages were included to control for pubertal development using three categories: 1) boys who were still in stage 1 (i.e. prepubertal) in both genital and pubic hair, 2) boys who were still in stage 1 of either genital or pubic hair development and in stage 2+ of the other, and 3) boys who were in stage 2+ of both genital and pubic hair development. All analyses were performed in R (R Core Team. 2018. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing).

3.4 Results

The majority women were Latina (97.7%) and born in Mexico (88.5%), with almost half having lived in the United States for less than five years at the time of the study child's birth (Table 1). Almost half had only a primary school education. Most of the boys were exclusively breastfed for at least two months (64.7%) and about half were considered normal weight at 12 years of age. Most of the boys had reached Tanner stage 2 or above in genital development (85.7%) by age 12, whereas pubic hair development was approximately split between Tanner stage 1 (46.4%) and Tanner stage 2 or above (53.6%).

The concentrations of detected PFR urinary metabolites ranged from <MLD to 23.8 ng/mL (Table 2). DPHP had the highest detection frequency (80.5%), followed by BDCIPP (78.2%). tbutylDPP had the lowest detection frequency of the four PFR metabolites measured (19.5%). The distributions seen in both the PFR detection frequencies and concentrations were similar to those observed in the larger CHAMACOS maternal cohort (N=310 mothers).[120]

FSH, LH, and testosterone levels in serum of the CHAMACOS boys at age 12 are shown in Table 3. Normal levels of FSH, LH, and testosterone vary widely during male puberty; however, the geometric means reported in Table 3 fall within normal ranges that have been previously reported for similar age ranges.[109,122–124]

PFR and hormone levels were also stratified by the puberty variable created for this study (Table 4). PFR metabolite levels did not vary much across the three puberty categories, but as expected, each hormone measured increased in concentration as puberty progressed (FSH: $p < 0.001$, LH: $p < 0.0005$, Testosterone: $p < 0.0005$).

The percent changes in each hormone level associated with a 10-fold increase in each PFR level from adjusted models are shown in Table 5. FSH levels increased as each PFR level increased, LH increased as BDCIPP and ipDPP increased and decreased as DPHP and tbutylDPP increased, and testosterone increased as each PFR increased with the exception of tbutylDPP. However, none of these associations were statistically significant. In the models adjusted for pre-pregnancy BMI and child's age at the 12-year hormone assessment, the largest effect observed was DPHP on FSH: for every 10-fold increase in DPHP, the FSH levels increased by 102.3%. This effect was followed by ipDPP on LH, ipDPP on testosterone, and BDCIPP on testosterone, all of which

had percent increases greater than 50%. We observed percent changes of greater than 50% between DPHP and FSH (102.3% increase, 95% CI: -12.1% to 370.1%), BDCIPP and testosterone (62.0% increase, 95% CI: -7.6% to 184.2%), ipDPP and LH (87.8% increase, 95% CI: -27.7% to 387.3%), and ipDPP and testosterone (71.8% increase, 95% CI: -35.3% to 356.0%).

Table 1. Characteristics of mothers and male children followed to 12 years of age

Maternal characteristics	**N (%)**
Age at delivery, years	
18-24	32 (36.8)
25-29	36 (41.4)
30-34	11 (12.6)
35-45	8 (9.2)
Education	
≤ 6th grade	42 (48.3)
7th – 12th grade	27 (31.0)
≥ High school	18 (20.7)
Race/ethnicity	
Latino	85 (97.7)
Other	2 (2.3)
Country of birth	
Mexico	77 (88.5)
U.S.	7 (8.0)
Other	3 (3.4)
Years in the U.S.	
≤ 1	21 (24.1)
2 – 5	21 (24.1)
6 – 10	24 (27.6)
≥ 11	15 (17.2)
Entire life	6 (6.9)
At or below Census poverty level at 12 years postpartum	
Yes	63 (72.4)
No	24 (27.6)
Parity	
0	24 (27.6)
≥ 1	63 (72.4)
Pre-pregnancy BMI (kg/m^2)	
< 18.5	2 (2.3)
18.5 – 24.9	27 (31.0)
25 – 29.9	36 (41.4)
≥ 30	22 (25.3)
Age of menarche, years	
< 12	39 (44.8)
12 – 13	17 (19.5)
> 13	31 (35.6)

Alcohol consumption during pregnancy	
Yes	19 (21.8)
No	68 (78.2)
Smoked during pregnancy	
Yes	2 (2.3)
No	85 (97.7)
Child characteristics	**N (%)**
At birth	
Low birthweight (< 2500 g)	
Yes	3 (3.4)
No	84 (96.6)
Exclusively breastfed, months	
< 2	55 (64.7)
2 – 6	20 (23.5)
> 6	10 (11.8)
At age 12	
BMI (kg/m^2)	
< 18.5	17 (19.5)
18.5 – 24.9	45 (51.7)
25 – 29.9	19 (21.8)
≥ 30	6 (6.9)
Tanner genital stage 2+	
Yes	72 (85.7)
No	12 (14.3)
Tanner pubic hair stage 2+	
Yes	39 (46.4)
No	45 (53.6)
Ever tried alcohol	
Yes	19 (21.8)
No	68 (78.2)
Ever smoked	
Yes	9 (10.3)
No	78 (89.7)

Table 2. Maternal prenatal urinary PFR metabolite levels in ng/mL (n =87)

PFR	> MDL (%)	Mean	GM (GSD)	p25	p50	p75	p90	p95	Max
DPHP	80.5	1.8	0.9 (2.9)	0.53	1.01	1.36	3.75	6.29	23.8
BDCIPP	78.2	0.70	0.3 (5.2)	0.11	0.33	0.99	1.64	2.25	4.9
ipDPP	66.7	0.45	0.3 (2.6)	<MDL	0.28	0.48	0.99	1.17	5.5
tbutylDPP	19.5	0.07	0.04 (3.2)	<MDL	<MDL	<MDL	0.16	0.20	1.0

Table 3. Hormone levels in boys, age 12

Hormone	N	Mean	GM (GSD)	Min	p10	p25	p50	p75	p90	p95	Max
FSH	87	2.8	2.5 (1.7)	0.65	1.2	1.8	2.6	3.5	4.7	5.2	9.5
LH	87	2.5	1.7 (3.3)	0.02	0.36	1.5	2.3	3.5	4.6	5.2	6.5
Testosterone	87	157	73.0 (4.2)	4.5	9.0	25.0	89.0	256	418	461	553

FSH and LH concentrations measured in mIU/mL of serum. Testosterone concentrations measured in ng/dL of serum.

Table 4. Geometric means and geometric standard deviations of maternal prenatal urinary PFR metabolites (ng/mL) and hormone levels in boys at age 12, stratified by puberty stages

	G1 & PH1 (n = 10)	G1/PH2+ or PH1/G2+ (n = 35)	G2+ & PH2+ (n = 38)
DPHP	0.8 (3.5)	0.9 (3.8)	1.0 (2.2)
BDCIPP	0.2 (5.9)	0.3 (6.1)	0.4 (3.9)
ipDPP	0.3 (2.6)	0.3 (2.4)	0.3 (2.8)
tbutylDPP	0.1 (2.4)	0.03 (2.4)	0.04 (3.9)
FSH*	1.5 (1.6)	2.3 (1.6)	3.1 (1.6)
LH*	0.4 (4.1)	1.6 (3.1)	2.9 (1.6)
Testosterone*	11.2 (1.9)	45.9 (3.2)	200 (2.6)

FSH and LH concentrations measured in mIU/mL of serum. Testosterone concentrations measured in ng/dL of serum.

* Significant differences among means of puberty groups from one-way ANOVA, $p < 0.05$

Table 5. Percent (%) change in hormone level for every 10-fold increase in PFR concentration and 95% confidence intervals (CI) from adjusted linear regressions for each association between each measured PFR in urine at 26 weeks gestations and hormone levels in boys at 12 years in the CHAMACOS cohort.

PFR	N	FSH (% change & CI)	LH (% change & CI)	Testosterone (% change & CI)
DPHP	87	102.3 (-12.9, 370.1)	-16.9 (-64.7, 95.8)	7.2 (-55.3, 157.2)
BDCIPP	87	15.8 (-33.7, 102.5)	15.1 (-34.2, 101.4)	62.0 (-7.6, 184.2)
ipDPP	87	21.0 (-53.8, 216.6)	87.8 (-27.7, 387.3)	71.8 (-35.3, 356.0)
tbutylDPP	87	23.6 (-44.4, 174.8)	-5.5 (-57.6, 110.5)	-32.1 (-69.9, 53.0)

All models include maternal pre-pregnancy BMI and child's age at time of 12-year hormone assessment.

After controlling for Tanner stages in the models, the effect size changed direction for LH and BDCIPP from increasing to decreasing, and for testosterone and DPP from increasing to decreasing, but associations were not statistically significant (See Supplemental Information, Table S1). Four boys were missing both Tanner stage information for genital and pubic hair development.

3.5 Discussion

Although our multivariate regressions did not yield any significant associations between any of the PFRs and any of the hormones, we did observe percent changes greater than 50% in some of the PFR-hormone relationships. Specifically, we observed percent changes of greater than 50% between DPHP and FSH (102.3% increase, 95% CI: -12.1% to 370.1%), BDCIPP and testosterone (62.0% increase, 95% CI: -7.6% to 184.2%), ipDPP and LH (87.8% increase, 95% CI: -27.7% to 387.3%), and ipDPP and testosterone (71.8% increase, 95% CI: -35.3% to 356.0%). Few studies have examined associations between exposures to PFRs and human health outcomes. Castorina et al. evaluated the association between prenatal urinary PFR levels and neurodevelopment in children 7 years of age from the same cohort as this study.[125] We did not observe any significant associations of prenatal maternal PFR concentrations in urine with FSH, LH, or testosterone, whether controlling or not for pubertal progression.

There are little to no known studies to corroborate or refute our results. Only one previous study assessed the relationship between PFRs and the same hormones, but evaluated PFRs in dust and hormones in *adult* males. Those researchers also observed an increase in FSH with increasing TPHP (the parent compound of DPHP) similar to our results, but contrary to our findings, saw a decrease in testosterone with increasing TDCIPP (the parent compound of BDCIPP).[117] However, their results were also not statistically significant. They did not measure isopropylphenol diphenyl phosphate (the parent compound of ipDPP). Results from other studies examining the relationship between brominated flame retardants and these hormones vary. Eskenazi et al. found increases in LH and testosterone in 12-year-old boys from the CHAMACOS study with increasing BDE-100 and BDE-153 levels[109] while another study found an inverse association between BDEs-47, -99, and -100 and FSH and LH in adult males.[9] Another study assessed adult male hormone concentrations and different commercial mixtures of PBDEs and found inverse associations with pentaBDEs and FSH, positive associations with octaBDEs and LH and testosterone, and an inverse association between decaBDEs and testosterone.[110]

3.5.1 Strengths and Limitations. The strengths of this study are its longitudinal design (the children in CHAMACOS have now been followed for seventeen years) and the analytical methods used to evaluate potential relationships between PFR metabolites and hormone concentrations. The main limitation of this study is the relatively small sample size – SOMETHING ABOUT POWER? PFR concentrations were not measured in the fetuses directly nor in the boys at 12-years of age. Additionally, prenatal urine samples were only measured during the mother's second trimester of pregnancy; however, there is evidence that spot urine samples for PFRs, namely BDCIPP and DPHP, collected during the mother's second trimester of pregnancy are consistent throughout pregnancy. A previous study found intraclass correlation coefficients for BDCIPP and DPHP to be 0.5 and 0.6, respectively, over the entire pregnancy.[126] Additionally, our study evaluated only male children and only at 12 years of age. To gain better understanding of reproductive development, future studies should follow both male and female children starting from pre-pubertal years to post-pubertal years.

3.5.2 Conclusions. Although there were no significant associations between PFR metabolites and hormones, there were marginally positive associations between DPHP and FSH and between

BDCIPP and testosterone. Elevated levels of FSH and testosterone in males have reproductive health implications. High FSH can lead to reduced sperm count and testicular failure.[127,128] Elevated testosterone levels can lead to irregular puberty.[129] TPHP and TDCIPP are two of the most widely used among current-use PFRs.[23] Indeed, TPHP and TDCIPP are found in almost all dust samples[130] and found on the same order of magnitude as PBDEs.[75,102] More research is required to further elucidate the health effects in humans to corroborate or refute the animal studies. The endocrine effects of TDCIPP and testosterone also should be further examined. Given that TPHP and TDCIPP are the most widely used OP flame retardants and that so little is known about their health effects, more research on this topic is crucial in order to advocate for safer alternatives and prevent regrettable substitutions.

3.6 Supplemental Information

Table S1. Percent (%) change in hormone level for every 10-fold increase in PFR concentration and 95% confidence intervals (CI) from adjusted linear regressions for each association between each measured PFR in urine at 26 weeks gestation and hormone levels in boys at 12 years in the CHAMACOS cohort, with models including pubertal status.

PFR	N	FSH (% change & CI)	LH (% change & CI)	Testosterone (% change & CI)
DPHP	83	98.6 (-12.6, 351.0)	-27.9 (-66.2, 53.5)	-11.2 (-54.2, 72.1)
BDCIPP	83	6.3 (-40.0, 88.2)	-13.0 (-48.2, 46.2)	10.5 (-29.8, 73.7)
ipDPP	83	24.3 (-52.3, 224.1)	124.6 (-4.3, 427.3)	99.5 (-5.2, 319.9)
tbutylDPP	83	28.6 (-43.7, 193.8)	-3.3 (-54.5, 105.5)	-29.7 (-63.4, 35.0)

All models include maternal pre-pregnancy BMI, child's age at time of 12-year hormone assessment, and pubertal status.

Chapter 4 – Including comparative chemical risk analyses with chemicals alternatives assessment in creating safer work environments: a case study in the electronics industry

4.1 Abstract

Chemical alternatives assessments are used to identify safer alternatives to chemicals of concern in industrial processes, products, and technologies. As public health concerns over occupational health and environmental health increase, industries (beginning with the textile and garment industry, and followed by the electronics industry) have more publicly began to move towards identifying safer chemicals in their manufacturing processes. However, a chemical alternatives assessment alone to identify safer alternatives to a chemical of concern may not be sufficient. This case study discusses the push within industry to use safer chemicals and conducts a risk assessment, supplementing a chemical alternatives assessment performed by an electronics company I collaborated with, to identify and compare safer alternatives to methylene chloride in a manufacturing process. This study also discusses the need to combine chemical alternatives assessments with risk assessments in identifying safer alternatives to chemicals of concern.

4.2 Introduction – The impetus for safer alternatives to chemicals of concern in industry

4.2.1 The textile and garment industry

The textile and garment industry is one of the oldest industries in the world and is also one of the largest employers in the world.[131] This industry provides the modern world with anything related to fabric, from the rugs that decorate our floors to the curtains that give our homes privacy to the shoes we wear. The textile and garment industry has largely been outsourced to developing countries where labor is cheap and regulations are lax or non-existent. The pull of cheap labor has resulted in unfair and unhealthy working conditions such as the use of sweatshops by companies like Nike that gained a lot of attention in the 1990s. Lenient regulations have led to unsafe working conditions such as the fire and building collapse of garment-producing factories within a span of six months in 2012-2013 in Bangladesh. Moreover, many laborers in the textile and garment industry are women and children.

In addition to using cheap labor, the textile and garment industry also uses many chemicals. Nearly 8,000 chemicals are used in the textile and garment industry across the supply chain, amounting to 5 billion kilograms (kg) of chemicals.[132] The chemicals used in textile and garment processing combined with the amount of water used by the industry results in highly toxic polluted wastewater that may run off from factories if not properly handled. This contaminated run-off can adversely impact ecological systems, particularly aquatic ecosystems. The last two decades saw the advent and burgeoning of fast fashion – a phenomenon in which haute-couture designs quickly move from high-fashion runways to stores where the designs are sold at lower prices for most consumers. Popularized and made readily available by retailers such as H&M, Target, Zara, and many more, fast fashion is churned out in multiple cycles rather than the traditional four seasons of fall, winter, spring, and summer. To accommodate fast fashion trends, production in the textile and garment industry must increase, potentially increasing the amount of wastewater runoff and creating more waste generally. With new fashion trends delivered at

inexpensive prices and offered more than four times a year, what once was new and trendy quickly becomes old and dated and therefore, discarded.

The chemicals used in textile and garment manufacturing processes are not only a concern for the environment, but also a concern for the workers who handle the chemicals and are exposed to them. Formaldehyde, a chemical classified as a known human carcinogen by the International Agency for Research on Cancer in 2004 and by the National Toxicology Program in 2011, is used in the textile and garment industry to treat clothing and to allow for better absorption of certain dyes. The National Institute for Occupational Safety and Health (NIOSH) conducted studies that linked exposure to formaldehyde in the garment industry to upper respiratory cancers and leukemia. Other studies have associated formaldehyde and other occupational exposures, to lung cancer [133], nasopharyngeal cancer [134], and spontaneous abortion.[135] Parental occupational exposures in the industry have even been linked to childhood cancers.[136]

The textile and garment industry began taking action in 2011 to identify safer alternatives to chemicals of concern after Greenpeace launched their DeTox campaign in 2010 to spotlight the water pollution associated with the industry and released "Dirty Laundry," a report that linked toxic water pollution to the textile and garment industry in China[137] and challenged the industry to take action in improving its environmental stewardship. This challenge resulted in the Zero Discharge of Hazardous Chemicals (ZDHC) initiative, starting with six brands in apparel and footwear that pledged to work towards severely reducing the textile and garment industry's emissions throughout its entire supply chain, from raw materials extraction to production to end-product disposal, by 2020. Currently, ZDHC has dozens of multi-stakeholder contributors, from the textile and garment industry to the chemical industry, who have committed to working towards zero emissions throughout their production chain. These efforts can be seen through H&M's clothes recycling program that collects disused clothes to prevent them from ending up in landfills[138] and Levi's waterless technology that produces denim using less water (Figure 1).[139]

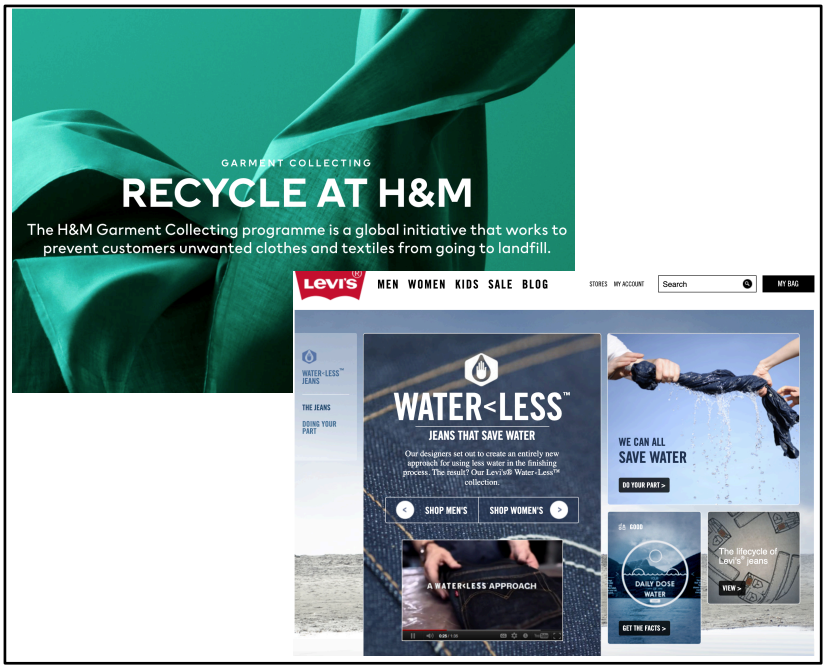

Figure 1. From their websites, Levi's waterless technology process for denim (foreground) and H&M's clothes recycling program.

While the ZDHC initiative is progressing towards zero hazardous emissions by 2020, its mission is solely to reduce hazardous chemical use to reduce emissions and does not address workers' rights or empowerment and the disproportionate number of women who labor within the textile and garment industry.

4.2.2 The electronics industry

The electronics industry has been one of the fastest growing industries in the contemporary world. From 1994 to 2004, the number of personal computers in the world increased from 20 million to 180 million, respectively.[140,141] The electronics industry is also responsible for the gadgets that the modern world uses on a daily basis to connect and to communicate with each other. The electronics industry produces laptop computers and mobile phones, as well as the semiconductors and micro-processing chips that power them. The smart technology powered by micro-processing chips has become so pervasive that any product with a micro-processing chip is now considered an electronic, including refrigerators and televisions. The electronics industry has paved the way for an advancing technological society, making it more convenient for economic markets to connect around the world, as well as for individuals to connect globally.

The first silicon transistors, the basis for semiconductors, were created in the 1950s where they were more commonly used in telephones and hearing aids. The semiconductor chip transformed the industry, allowing room-sized computers from the 1950s to shrink in size to the razor-thin laptops consumers use today.[142] Millions of chips are made for the millions of electronics in the market. The industry flourished in California's Bay Area, a region south of San Francisco that has come to be known as the Silicon Valley because of the electronics industry's presence and growth there. For the past two decades, people have poured into the Silicon Valley to take

advantage of the employment opportunities. The electronics industry now employs workers all over the world.[143]

The ability to have information at our fingertips is astronomical, but there is a downside to this ability – the potential damage to human health – that is often overlooked by the damage done to society in which the electronics industry is also complicit. The industry's public relations campaign strove to maintain its reputation as a clean industry with images of workers in clean rooms wearing protective clothing (to protect the processes and not necessarily the workers).[143] Contrast the clean laboratory scene of the electronics industry to that of factories emitting clouds of fume from industries traditionally thought of as dirty like the steel industry, and even the textile and garment industry, and it is not difficult to see how the electronics industry maintained a public reputation as clean and safe.[142,144]

The electronics industry largely avoided consideration as a public health problem until stories of health problems in the region where it housed itself made their way into the news in the 1980s.[142,144] For example, in 1980, IBM discovered a leak in a storage tank, contaminating groundwater around the plant in South San Jose, California, with trichloroethylene, a suspected carcinogen, and other chemicals.[145] In 1981, Fairchild Semiconductor in San Jose, California, discovered a hole in one of their solvent tanks that leaked all 55 thousand gallons of its 1,1,1-trichloroethane (a trichloroethylene substitute), acetone, and xylene mixture into the ground and contaminated an adjacent drinking well.[142,144,145] These discoveries occurred at the same time a neighboring community began noticing and voicing concerns over an excess number of birth defects, miscarriages, and stillbirths. Indeed, studies conducted by the California Department of Public Health showed the San Jose community exposed to the contaminated drinking well had increased cases of spontaneous abortion, congenital birth malformations, and cardiac birth anomalies.[146,147] Under intense public pressure, California's Regional Water Quality Board surveyed the soil and water around other storage tanks in the area and found that 75 percent of tanks had contaminated the surrounding soil or groundwater.[144,148] The United States Environmental Protection Agency (US EPA) also responded to the pressure by designating 19 Silicon Valley sites as Superfund sites, locations in the United States contaminated by hazardous waste that the US EPA identifies as contenders for remediation because of risks to human and environmental health,[149] in 1984. 19 sites eventually grew to 29 sites before the close of the decade, giving the Silicon Valley the highest concentration of US EPA Superfund designations in one region at the time.[144,150]

In addition to environmental pollution and potential health risks of neighboring community members, workers in the electronics industry may also be at risk for health effects. Similar to the textile and garment industry, the electronics industry makes use of a wide range of chemicals.[142] Suspected carcinogens such as the aforementioned trichloroethylene, methylene chloride, and perchloroethylene are used in many electronics manufacturing processes.[151–153] A series of epidemiological studies evaluated the association between adverse reproductive health outcomes, cancer, and other rare diseases to semiconductor work in the United States,[154–156] Taiwan,[157–159] Korea,[160–163] and other regions.[164–167] While the studies reported mixed results, the evidence suggested increased spontaneous abortion and excess risks for non-Hodgkin's lymphoma, leukemia, brain tumors, and breast cancer for these workers.[168] South Korean electronics brand and original equipment manufacturer (OEM) Samsung has even made international headlines as

recently as in 2018 for admitting responsibility for the sickness of their production line workers and issuing an apology.[169]

In fact, campaigns for safer work practices and reduced toxics in the electronics industry has been led by labor activists, from the Silicon Valley Toxics Coalition in California to the Supporters for the Health and Rights of People in the Semiconductor industry in South Korea.[144,170] As the public becomes increasingly aware of the toxic chemicals used in the electronics industry, organizational campaigns have mobilized to pressure the electronics industry to take responsibility for its environmental and occupational health stewardship. Electronics companies house chemical management departments that search for safer alternatives to chemicals of concern as part of their program. These efforts are now partially publicized and are made available on the websites of companies such as HP[171,172] and Apple[173] (Figure 2). Like the textile and garment industry before it, the electronics industry is engaging in multiple stakeholder groups to address environmental and labor rights issues.

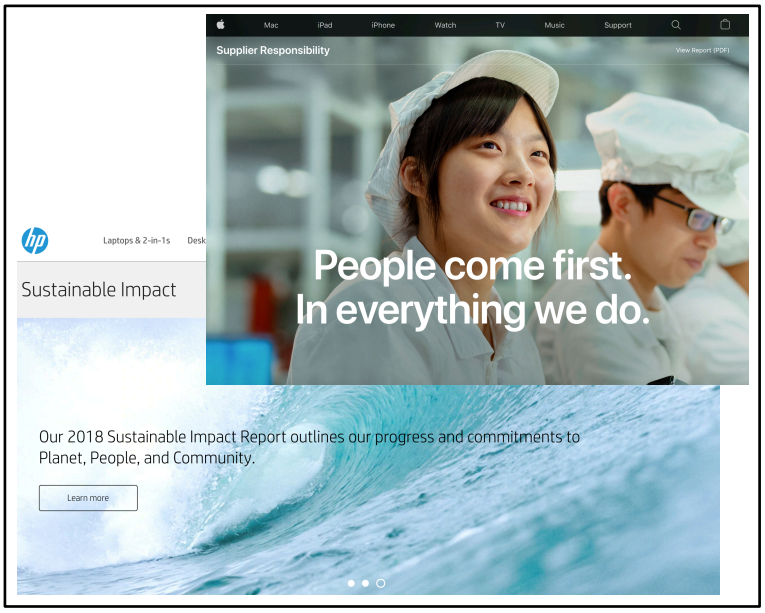

Figure 2. Apple's supplier responsibility webpage with access to annual reports (foreground) and Hewlett Packard's sustainable impact webpage, also with access to annual reports.

The objective of one such multi-stakeholder network with whom I collaborated is to achieve zero exposure of workers to toxic chemicals in the electronics manufacturing process. The network aims to achieve this goal through four working initiatives, one initiative is substituting identified chemicals of concern with safer alternatives. Utilizing a chemical alternatives assessment, a participant member in this network identified a potassium hydroxide mixture as a safer alternative to methylene chloride for a process involving removal of a residue known as PEHD from metal parts. While the chemical alternatives assessment identified the potassium hydroxide mixture as a safer alternative with a lower hazard profile, it did not compare the human health risks between potassium hydroxide and methylene chloride. The remainder of this chapter discusses the benefits of including comparative risk analyses to further inform and strengthen

selection and implementation of safer alternatives, highlighting this methylene chloride case study as an example.

4.3 Chemicals alternatives assessments and comparative risk analyses

4.3.1 Regrettable substitutions

The increasing evidence and acknowledgement of worker exposure to toxic chemicals in the electronics industry has led to the subsequent demand of safer alternatives to chemicals of concern (i.e., chemicals suspected to be harmful to human health or the environment). However, replacement chemicals have not always solved the problem at hand and have instead, resulted in regrettable substitutions. A regrettable substitution is replacing a chemical of concern with a chemical that has the same harmful qualities or worse. One of the most infamous cases of regrettable substitutions resulted from the California ban on chlorinated solvents in aerosol products in 2000.[174] Manufacturers replaced perchloroethylene, a chlorinated solvent used in automotive brake cleaners, with n-hexane. However, increased cases of automotive technicians visiting emergency rooms for peripheral neuropathy emerged resulting from exposure to n-hexane.[175,176] This outcome was predictable given that the neuropathic effects of n-hexane had been known since the 1960s.[177]

Stories like these are rife in chemical history. Dichloro-diphenyl-trichloroethane (DDT) was banned in 1972 because of its environmental and toxicological effects[178] and replaced with the neurotoxic organophosphate pesticides.[179–182] Bisphenol A (BPA), a chemical commonly used in plastics and an endocrine disruptor,[183] was replaced with bisphenol S, BPA's chemical cousin and suspected to have similar health effects as BPA.[184–186] Within the electronics industry, the suspected carcinogen trichloroethylene was replaced with 1,1,1-trichloroethane.[145,187,188] 1,1,1-trichloroethane was the main groundwater contaminant that was associated with adverse reproductive health outcomes in the Silicon Valley. Despite being suspected as a carcinogen, trichloroethylene would be listed as an acceptable alternative to 1,1,1-trichloroethane by the US EPA in 1993.[187]

Without proper evaluation of a chemical alternative that is chosen to replace a chemical of concern, the alternative itself can become a chemical of concern. Sometimes, it is already a chemical of concern as was the case with n-hexane. In the search for safer alternatives to chemicals of concern, a major endpoint is to avoid regrettable substitutions. To avoid these types of regrettable substitutions, approaches like chemical alternatives assessments exist to evaluate and compare the potential harmful effects of alternatives to make an informed substitution. The remainder of this chapter discusses including a risk assessment framework with a chemical alternatives assessment to avoid such regrettable substitutions.

4.3.2 Chemical alternatives assessments

A chemical alternatives assessment is a methodology used to identify, compare, and select safer alternatives to replace chemicals of concern in processes, materials, or technologies. Chemical alternatives assessments utilize a hazard approach to identify and compare safer alternatives. They identify and compare the hazards of each alternative. This approach assumes that if there is

little to no hazard, then there is little to no risk. Each chemical alternatives assessment may be adapted to fit the needs of its users (whether they be businesses, governments, or non-governmental organizations), but underlying each chemical alternatives assessment is the common principle to reduce harm to human health and the environment, and avoid regrettable substitutions. A chemical alternatives assessment should thoroughly consider the hazard profile, performance value, and economic viability of an alternative throughout its entire life cycle.[189–191]

The methylene chloride case study referenced above employed a chemical alternatives assessment, adapted from the National Academy of Sciences' and the California Department of Toxic Substances Control's frameworks,[192,193] to identify the potassium hydroxide mixture as a safer alternative to methylene chloride. An overview of this chemical alternatives assessment process is presented in Figure 3.

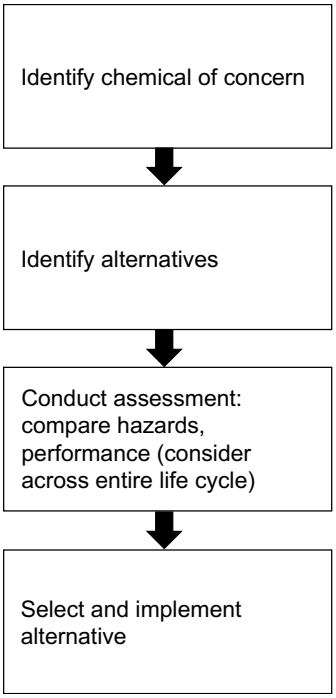

Figure 3. Process overview of chemical alternatives assessment used for the methylene chloride case study.

These steps involve:

1) *Identify the chemical of concern* – This step includes defining the scope and goal of the chemical alternatives assessment and characterizing the chemical of concern.
2) *Identify the alternatives* – After understanding and confirming the functional use of the chemical of concern, alternatives are identified by understanding available information. Alternatives can be identified through internet searches, market surveys, conversations with chemicals manufacturers, and literature reviews, etc.

3) *Conduct comparative assessments* – This step includes comparing the hazards, performances, and cost-effectiveness of identified alternatives. Health and environmental impacts at all stages throughout each alternatives life cycles should be considered in this step.
4) *Select and implement alternative* – Once an alternative is identified, it needs to be adopted into its application. This may include disseminating information to applicable facilities that need to implement the alternative and require process changes, further testing, and investment in time and resources.

Similar to other chemical alternatives assessments, this methylene case study followed a hazards approach to identify the potassium hydroxide mixture as a safer alternative. While the potassium hydroxide mixture was chosen because it has a lower hazard profile than methylene chloride, this assessment did not analyze risk, thereby overlooking the magnitude of potential health effects through different exposure pathways. Potassium hydroxide is known to corrode tissue on contact, whereas methylene chloride is a suspected carcinogen and associated with central nervous system toxicity. The chemical alternatives assessment alone cannot determine the likelihood of adverse outcomes from exposure to either of these materials or compare the magnitude of adverse events resulting from these exposures. These metrics require additional exposure assessments and exposure-response assessments, which are built into the risk assessment paradigm.

4.3.3 Risk assessments and comparative risk analyses

Risk assessments are used in the environmental health sciences to calculate magnitude of health risk from exposures, which are, in turn, used to determine exposure limits. Different governmental regulatory agencies employ risk assessments.[194] Figure 4 illustrates the National Institute for Occupational Safety and Health's (NIOSH's) risk assessment process.

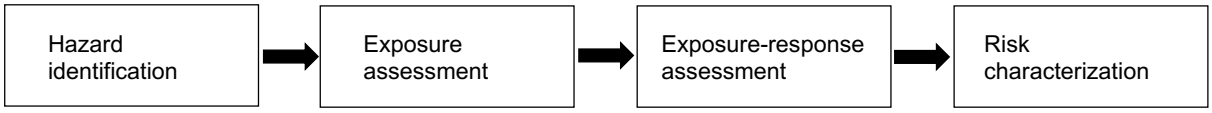

Figure 4. Process overview of NIOSH risk assessment.

These steps involve:

1) *Hazard identification*. A risk assessment begins with identifying hazards. In this step, potential health effects of the chemical of concern are evaluated. Toxicological data weighing the strength and nature of potential health effects are collected to determine which health effects to include in the risk assessment.
2) *Exposure assessment*. Exposure assessments measure the magnitude of occupational exposure to chemicals. They are necessary to understand the frequency, duration, and intensity of occupational exposures through different exposure routes. The most common and most likely routes of occupational exposure are inhalation and dermal contact.

3) *Exposure-response assessment.* The exposure-response assessment evaluates exposure levels and the health effects that are observed at those exposure levels. This step produces a reference concentration (for air levels) or a reference dose (for ingestion levels) for non-cancer outcomes and a unit risk for cancer endpoints. The reference concentration is a concentration of exposure that is likely to not produce significant adverse health effects for non-cancer endpoints during a lifetime. The unit risk for cancer endpoints calculates the risk of cancer given an exposure concentration.
4) *Risk characterization.* Using the hazard and exposure information gathered from the previous steps, the likelihood or magnitude of an adverse event from inhalation exposure, non-cancer or cancer, can be calculated to inform risk management programs. For non-cancer endpoints, one way to characterize risk is through hazard quotients, which are calculated using Equation 1.

(Equation 1) $$HQ = \frac{EC}{RfC}$$

HQ = hazard quotient
EC = exposure concentration
RfC = reference concentration

When a hazard quotient is greater than one, the chemical is considered to be more likely to cause an adverse outcome. Alternatively, when a hazard quotient is less than one, the chemical is considered as less likely to cause an adverse outcome. The hazard quotient is not a probability, but an indication of potential for adverse health effects and it does not provide information on how much that potential increases or decreases.[195]

For cancer endpoints, risks are calculated using Equation 2.

(Equation 2) $$CR = IUR \times EC$$

CR = cancer risk
IUR = inhalation unit risk
EC = exposure concentration

A comparative risk analysis would take the risk calculation or characterization from each chemical risk assessment and compare them to each other.

4.3.3.1 Comparative risk analysis of methylene chloride and potassium hydroxide

To supplement the results from the chemical alternatives assessment conducted by the electronics company and to further understand the risks associated with the different exposure pathways of methylene chloride and potassium hydroxide, I conducted a comparative risk analysis to compare the risks of methylene chloride and potassium hydroxide using existing data. The original methylene chloride case study also evaluated benzyl alcohol as an alternative; however, benzyl alcohol did not perform well in the metal cleaning application and so was not

considered further for the chemical alternatives assessment. For this reason, I also excluded benzyl alcohol from this comparative risk analysis. Only inhalation and dermal contact exposure routes were evaluated, as these are the mostly likely routes of exposure in an occupational setting.

Hazard identification. Methylene chloride and potassium hydroxide have been associated with a number of acute and chronic health endpoints, summarized below and in Table 1:

Methylene chloride. Short-term inhalation exposure to methylene chloride is associated with central nervous system toxicity, which includes dizziness, clumsiness, headache, nausea, and tingling or numbness of fingers and toes. This collection of neurological effects are the most often reported adverse human health outcomes associated with methylene chloride exposure.[196] Short-term inhalation exposure to methylene chloride can also irritate the upper respiratory system and result in shortness of breath, coughing, chest tightness, and asphyxiation.[196] Short-term contact to the skin and eyes can also result in skin and eye irritation.[196] In some cases, chemical burns developed on areas where methylene chloride came in contact with the skin.[197–199] Acute inhalation exposure to methylene chloride (one to three hours of exposure) has even resulted in death where there was poor ventilation.[197,199–207]

Chronic inhalation exposure to methylene chloride can result in memory loss, reduced attentiveness, personality changes, and depression.[208,209] Long-term exposure has also been associated with reduced fertility and reduced sperm counts in men,[208] and spontaneous abortions in women.[210] Damage to the liver and kidneys has been observed in animal studies from intermediate and chronic exposures to methylene chloride.[211–219] Human studies have not shown any association to organ toxicity from intermediate or chronic exposures, but studies are limited.[196] Long-term exposure to methylene chloride does not appear to increase death rates.[220–222] Epidemiologic studies also provide evidence that chronic inhalation exposure to methylene chloride is associated with increased risks of brain cancer, multiple myeloma, biliary cancer, liver cancer, non-Hodgkin's lymphoma, and breast cancer among women.[196,223,224] The International Agency for Research on Cancer (IARC) and the United States National Toxicology Program (US NTP) both classify methylene chloride as a possible human carcinogen.[225,226] Repeated skin contact can result in contact dermatitis.[196]

Potassium hydroxide. Short-term inhalation exposures to potassium hydroxide can result in upper respiratory tract irritation.[227,228] Dermal contact with solutions containing at least two percent potassium hydroxide corrodes tissues resulting in skin lesions.[227–229] Eye irritation can also occur from contact with potassium hydroxide dust or mist.[227,228]

Chronic inhalation exposure to potassium hydroxide is associated with narrowing of the esophagus.[228] Repeated dermal contact with potassium hydroxide can result in dermatitis.[228]

Table 1. Hazards comparison between methylene chloride and potassium hydroxide

	Carcinogenicity	Central nervous system toxicity	Reproductive toxicity	Tissue corrosion	Contact dermatitis	Upper respiratory tract irritation	Skin irritation	Eye irritation
Methylene chloride	x	x	x			x	x	x
Potassium hydroxide				x	x	x	x	x

For this comparative risk analysis, I chose to focus on those health effects most well-known or suspected for each chemical, or health effects where there was enough data to calculate risk. These health effects were cancer and non-cancer endpoints for methylene chloride, and skin corrosion and upper respiratory irritation for potassium hydroxide.

Exposure-response assessment. Risk assessments for methylene chloride have been previously conducted and the US EPA lists a reference concentration for non-cancer endpoints with inhalation exposure, and an inhalation unit risk for cancer endpoints. The European Chemicals Agency (ECHA) lists a reference concentration for non-cancer endpoints from inhalation exposure to potassium hydroxide.[230] A reference concentration for dermal exposure does not exist for potassium hydroxide, but I used the results from a study that determined the concentration at which potassium hydroxide results in tissue corrosion (a binary outcome) from exposure to 0.5 milliliters (mL) of solution.[229] These reference concentrations are listed in Table 2.

Table 2. Reference concentrations for non-cancer and cancer endpoints from inhalation and dermal exposure to methylene chloride and potassium hydroxide

	Methylene chloride	Potassium hydroxide
Non-cancer (inhalation)	6×10^{-1} mg/m^3	1 mg/m^3
Cancer (inhalation)	1×10^{-8} per μg/m^3	n/a
Skin corrosion (dermal)	n/a	2% in solution

Exposure assessment. Exposure assessments for methylene chloride and potassium hydroxide are lacking and especially so for this specific occupational setting. Therefore, I assumed a worst-case scenario for both chemicals using occupational exposure limits set by either governmental organizations or electronic brand. These exposure limits are displayed in Table 3, with the chosen exposure concentration utilized for the subsequent risk characterization in bolded characters.

Table 3. Occupational Exposure Limits

	OSHA	NIOSH	ACGIH TLV	Internal limit*
Methylene Chloride	PEL - 25 ppm (TWA), 125 ppm (ST)	REL - 25 ppm (TWA)	TWA - 50 ppm	**Ceiling - 1000 ppm**
Potassium hydroxide	Ceiling - 2 mg/m^3	Ceiling - 2 mg/m^3	Ceiling - 2 mg/m^3	n/a

OSHA – Occupational Safety and Health Administration
ACGIH – American Conference of Governmental Industrial Hygienists
PEL – Permissible exposure limit
TWA – Time-weighted average (average exposure over an 8-hour period)
ST – Short-term
REL – Recommended exposure limit
TLV – Threshold limit value
*Occupational exposure limit from an electronic brand's manufacturing restricted substances list

Risk characterization. I assumed a worst-case scenario for each chemical, using the highest concentration limit set by a governmental agency or brand for exposure concentration. In this worst-case scenario, I also assumed the worker was not appropriately protected with personal protective equipment (i.e., no respirator, no gloves, no safety goggles). Table 4 presents the hazard quotients and risks calculated.

Table 4. Comparative risk characterization of methylene chloride and potassium hydroxide

	Methylene chloride	Potassium hydroxide
Hazard quotient	5783	2
Cancer risk	0.03	n/a
Skin corrosion risk	n/a	> 0.33*

*To calculate the risk of skin corrosion from exposure to potassium hydroxide, I used the quantitative data from Vernot et al.[229] to determine skin corrosion from potassium hydroxide solutions. The study determined a solution was corrosive to skin if at least two out of six of the rabbits tested developed skin corrosion after exposure to 0.5 mL of the potassium hydroxide solution. This criteria occurred with a solution that was 2% potassium hydroxide. The potassium hydroxide mixture that was chosen as the alternative to methylene chloride was 40% potassium hydroxide. The risk associated with skin corrosion was determined by the number of rabbits that developed skin corrosion; in this case, at least two out of six.

4.4 Challenges to and recommendations for incorporating comparative risk analyses with chemical alternatives assessments

4.4.1 Challenges

There are many challenges when identifying and implementing safer alternatives to chemicals of concern within the context of chemical alternatives assessments. The biggest challenge in

conducting chemical alternatives assessments is the scarcity of data.[190] This challenge also applies to risk assessments and supplementing chemical alternatives assessments with comparative risk analyses will only amplify existing data gaps. This is evident in the previous comparative risk analysis where the lack of consistently designated reference concentrations provides tenuous risk comparisons. The lack of exposure data also creates difficulties in calculating more likely risks rather than relying on worst-case scenarios.

Another challenge resides in deciding how to weigh risks. In the worst-case scenario analysis described in the previous section, the risk of cancer from inhalation exposure to methylene chloride is 0.03 whereas the risk of skin corrosion from dermal exposure to potassium hydroxide is at least 0.33. Cancer is considered the more hazardous health endpoint, but the risk of workers developing it is at least one magnitude less than the risk of workers getting skin corrosion. However, these risks may not be comparable because of the different risk characterization approaches to cancer and non-cancer outcomes. Deciding if more workers getting a presumably less hazardous health outcome is a challenge companies should address and justify.

An additional challenge to incorporating comparative risk analyses with chemical alternatives assessments is implementation and compliance. Like the textile and garment industry, the electronics industry also outsources much of its manufacturing to other countries to take advantage of cheap labor and less stringent safety regulations. A brand, also known as an original equipment manufacturer (OEM), can have contractors that have their own operations that further contract out their work to sub-contractors that also have separate operations that the brand or OEM may not even know about (Figure 5). With this level of outsourcing, decisions about processing made at the brand or OEM level are even more difficult to implement and regulate, especially if Tier 2 or further sub-contractors lack the resources such as industrial hygienists to regulate worker safety.

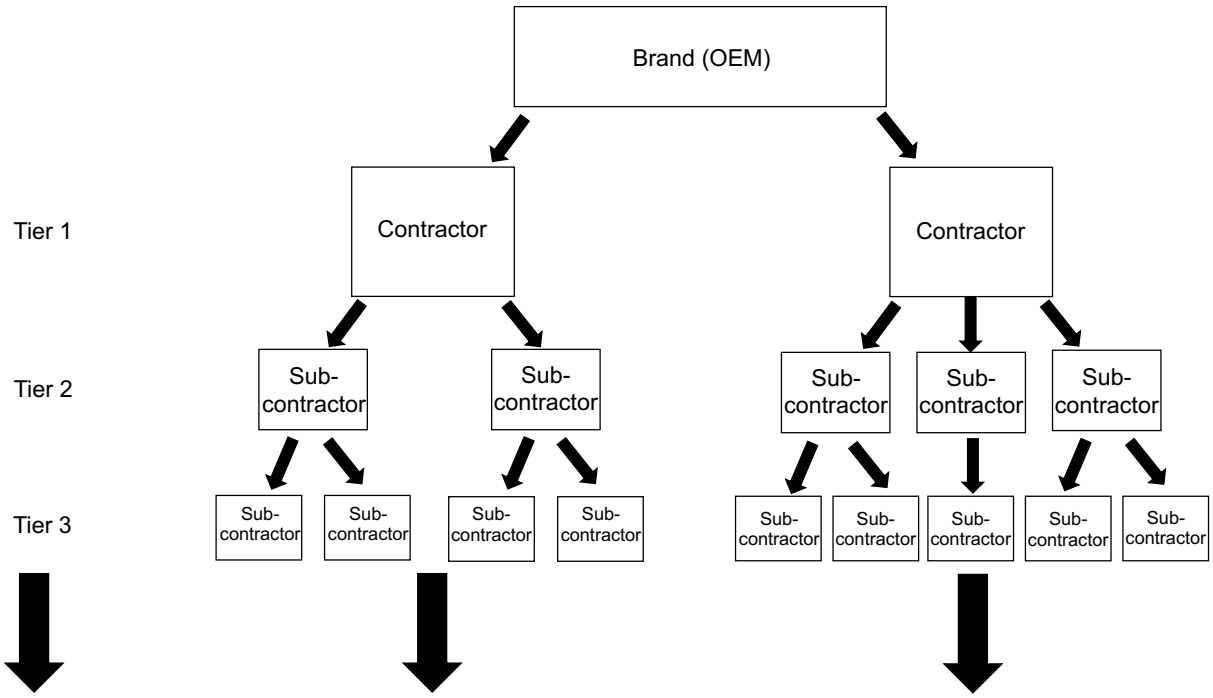

Figure 5. Schematic of electronics manufacturing outsourcing.

4.4.2 Recommendations

The European Chemicals Agency oversees the safe use of chemicals in Europe and governs the European Union Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program. The REACH regulation is in charge of protecting human health and the environment from risks introduced from chemicals. Any chemical manufactured or imported over one ton annually into the European Union must be registered under REACH. REACH places the onus on industry to identify and manage risks of any chemicals brought into the European Union; this includes conducting hazard assessments and risk assessments. This is in contrast to the United States, which places the burden of proof on the US EPA rather than on industry.

In the absence of regulation like REACH in the United States, electronics companies are adopting their own methods to evaluate chemical safety in response to growing public awareness and concern. As part of this effort, companies should mimic REACH and adopt comparative risk analyses as part of their chemical alternatives assessment. If enough data is available, companies will need to determine which risks weigh more heavily if hazards and risks increase at different rates. In the methylene chloride case study, the company would need to decide whether to put more weight to a lower risk of a higher hazard than a higher risk of a lower hazard. These weights can be determined during the scoping step of a chemical alternatives assessment. Given the challenges to completing traditional risk assessments that calculate probability because of data gaps, qualitative risk assessments could be utilized to compare risks. In qualitative risk assessments, probability of risk would be determined with historical data and categorized using qualifiers such as “high likelihood or severity” and “low likelihood or severity” rather than by quantitative estimates. These qualifiers could be visually represented in a matrix to decide which alternative to substitute the chemical of concern (Figure 6).

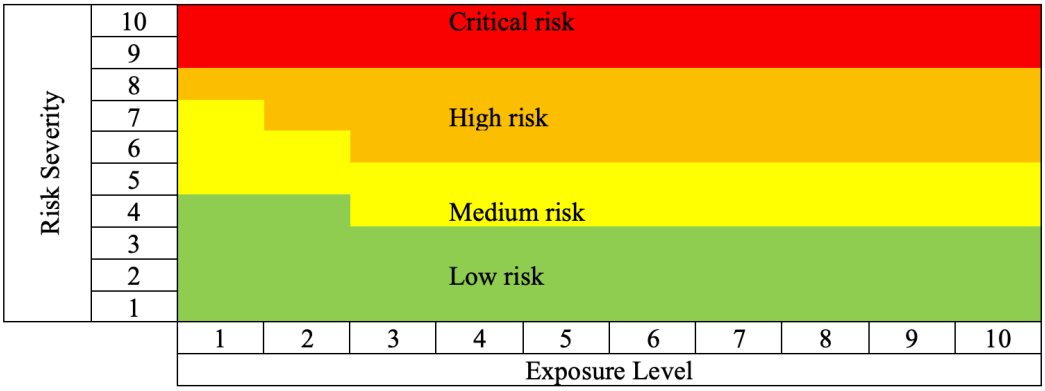

Figure 6. A potential matrix to compare and rank chemical risks, modeled after the design failure mode and effect analysis matrix.

If a chosen alternative still has some level of risk, a risk assessment conducted on that alternative would determine a reasonable occupational exposure limit and inform exposure prevention efforts to implement appropriate controls. However, this would require data, and so in addition to supplementing chemical alternatives assessments with risk assessments, increased exposure monitoring needs to be in place in manufacturing facilities.

4.5 Conclusions

Risk assessments are often considered unrealistic and time-intensive within the context of identifying and choosing safer chemicals,[231] but in order to fulfill the goal of a chemical alternatives assessment to "minimize the potential for unintended consequences, like those that result from switching to a poorly understood (and potentially more hazardous) substitute"[189] and make informed substitutions by reducing risk,[189–191] risk needs to be fully understood. This cannot be done by hazard alone because risk is a function of hazard and exposure. To fully understand and reduce risk, risk assessments should be a necessary component of chemical alternatives assessments to truly inform decision-making and safer substitutions, and for risk assessments to be conducted, data is required. Most of the chemicals in use today are poorly understood because safety testing was not and still is not required during chemical synthesis in the United States. The burden of proof to prove a chemical's safety should be placed on industry, as the European Union's REACH regulation does, and not on governmental agencies. While the contents of this chapter only focused on occupational health, the health and environmental impacts along the entire life cycle of any alternatives must also be considered so as not to shift the burden of impact from one stage to another. This includes conducting environmental health risk assessments in addition to chemical alternatives assessments where occupational health is not the focus.

With chemical regulations such as REACH in place, it makes business sense to follow sustainable practices; if United States chemical manufacturers want to maintain a business presence in Europe, they will need to follow REACH's guidelines.[232] Compared to the textile and garment industry, the electronics industry is years ahead in addressing the health and environmental impacts of its processes. However, because industries have failed to consider the

precautionary principle, the electronics industry suffers from the same lack of data to comprehensively conduct chemical alternatives assessments and risk assessments. The electronics industry and other industries have a real opportunity to pave the way towards innovation and more sustainable production.

Chapter 5 – Discussion

In this dissertation, I set out to map a typical chemical's journey through the United States chemical management system through the previous three research projects. As legacy chemicals are banned or phased out because of increasing evidence associating them with detrimental health effects, emerging chemicals that are often not studied beforehand replace the legacy chemicals and the cycle repeats. As more and more research come out with evidence of negative health effects, the public becomes increasingly aware of these issues and campaigns to make consumer products and manufacturing of these products safer bloom into existence. As pressure grows from outside forces, industry takes steps to find safer substitutions for whatever chemical is currently in the spotlight. My dissertation research represents these stages in a chemical's journey beginning with current contamination levels of an emerging flame retardant (PFRs), followed by an evaluation of potential health effects of the emerging flame retardant, and closing with a discussion on the steps industry has taken to address increasing concern over the health and environmental effects of chemicals used in their manufacturing processes and the challenges they face because of a lack of appropriate chemical regulation.

5.1 Summary of findings

5.1.1 Organophosphate flame retardants in fire station dust

The second chapter was a follow-up study to the FOX study that found elevated levels of the legacy flame retardant, PBDEs, in California fire station house dust in relation to other residential and occupational settings. This Fire Station Dust Study measured the legacy flame retardants, PBDEs, and the re-emerging flame retardants, organophosphate flame retardants, that are replacing PBDEs to meet fire safety standards in fire station dust across the United States. Some of the PFRs in dust were found on the same order of magnitude as some of the PBDEs and both were found at higher concentrations in fire station dust than other residential and occupational settings. The high concentrations of both organophosphate and PBDE flame retardants in fire station dust illustrate the need to identify and control for the sources of flame retardant contamination in fire stations. The elevated levels also underscore the fact that even though PBDEs are phased out, they are persistent and still contaminate many microenvironments where people are exposed. PFRs are also found on the same level as PBDEs underscoring the fact that fire station contamination is already high for a chemical about which we do not fully understand the health effects.

5.1.2 Organophosphate flame retardants and male sex hormones

Though organophosphate flame retardants have been around for decades, they are now reemerging as replacement flame retardants for the phased-out PBDEs. The third chapter looked at the association between prenatal maternal levels of urinary PFR metabolites and levels of sex hormones in male children aged 12 in the CHAMACOS cohort. The results indicated that the main PFRs found in the FireMaster formulation, TPHP and TDCIPP, were associated with an increase in FSH and a decrease in testosterone, respectively, albeit not significantly. Despite the non-significance of these associations, much is still largely unknown about these replacement

flame retardants that, as shown in the previous chapter, are already contaminating microenvironments at high concentrations.

5.1.3 Combining risk and alternatives assessments to find safer substitutions for chemicals of concern

In the fourth chapter, I highlight the role the electronics industry has taken to bridge the gap between older iterations of chemical innovation and public health and discuss the role of risk assessments in alternatives assessments and the challenges to completing risk assessments as observed through a comparative risk analysis I conducted to replace a chemical of concern within the electronics industry. Though risk assessments are considered an unrealistic approach to finding alternatives for chemicals of concern, they can still play an important role in identifying safer chemicals. If the alternatives in consideration are already existing chemicals that have been understudied, a risk assessment would greatly improve on a chemical alternatives assessment by providing the data needed to understand and characterize their human and environmental health risks. Risk assessments are also useful in creating standards for exposure and can keep original equipment manufacturers accountable for chemicals of concern that maintain a place on their manufacturing floors that are more difficult to replace because of a lack of suitable alternatives. It should be clear that a lack of suitable alternatives should not be a pass to continue using the chemical of concern, but instead a call to drive innovation using alternatives assessments to identify and use safer alternatives. Risk assessments should be performed periodically along with exposure assessments to ensure workers are not overexposed and emissions are under control.

5.2 Conclusions

Fire fighters are potentially exposed to elevated PFR concentrations in dust. The sources of these high concentrations need to be investigated to reduce their exposures and mitigate the already high chemical exposures experienced by fire fighters. Toxicological studies on PFRs have conflicting evidence and human health studies on PFRs are few and far between. PFRs are already seen on the same level of contamination as PBDEs and we don't know enough about the health effects of these replacement flame retardants. This issue is not isolated to flame retardant chemicals. As seen through the electronics industry, solvents used in process manufacturing that have long been associated with acute and chronic health effects are being reevaluated for safer alternatives. Some of these alternatives are existing chemicals that have not been assessed in the same way as the chemicals of concern and so risk assessments should still be conducted in concert with alternatives assessments in finding safer substitutions.

Chemical management in the United States is complex and difficult to enforce. These intricacies often result in replacing problem chemicals with understudied chemicals that can be potential regrettable substitutions. While the research I laid out still needs to be done, research invoking the precautionary principle also needs to take place before more chemicals are created that can damage human and environmental health systems. Moreover, this principle should be applied to the entire life cycle of a chemical to avoid burden-shifting to another stage in the life cycle. We have had decades to see this pattern. It is unnecessary to wait another decade or more to see the safe use of chemicals.

References

1. Kriebel, D.; Tickner, J.; Epstein, P.; Lemons, J.; Levins, R.; Loechler, E. L.; Quinn, M.; Rudel, R.; Schettler, T.; Stoto, M. The precautionary principle in environmental science. *Environ. Health Perspect.* **2001**, *109* (9), 871–876.
2. Sjödin, A.; Patterson, D. G., Jr.; Bergman, A. A review on human exposure to brominated flame retardants--particularly polybrominated diphenyl ethers. *Environ. Int.* **2003**, *29* (6), 829-839.
3. Segev, O.; Kushmaro, A.; Brenner, A. Environmental impact of flame retardants (persistence and biodegradability). *Int. J. Environ. Res. Public Health.* **2009**, *6* (2), 478-491.
4. U. S. EPA. Technical Fact Sheet - Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs). U. S. Environmental Protection Agency, Washington, DC, EPA 505-F-14-006, **2014**.
5. Zhang, X. L.; Luo, X. J.; Liu, H. Y.; Yu, L. H.; Chen, S. J.; Mai, B. X. Bioaccumulation of several brominated flame retardants and dechlorane plus in waterbirds from an e-waste recycling region in South China: associated with trophic level and diet sources. *Environ. Sci. Technol.* **2010**, *45* (2), 400-405.
6. Waszak, I.; Dabrowska, H.; Gora, A. Bioaccumulation of polybrominated diphenyl ethers (PBDEs) in flounder (Platichthys flesus) in the southern Baltic Sea. *Mar. Environ. Res.* **2012**, *79*, 132-141.
7. Chao, H. R.; Shy, C. G.; Wang, S. L.; Chih-Cheng Chen, S.; Koh, T. W.; Chen, F. A.; Chang-Chien, G. P.; Tsou, T. C. Impact of non-occupational exposure to polybrominated diphenyl ethers on menstruation characteristics of reproductive-age females. *Environ. Int.* **2010**, *36* (7), 728-735.
8. Harley, K. G.; Marks, A. R.; Chevrier, J.; Bradman, A.; Sjödin, A.; Eskenazi, B. PBDE concentrations in women's serum and fecundability. *Environ. Health Perspect.* **2010**, *118* (5), 699-704.
9. Meeker, J. D.; Johnson, P. I.; Camann, D.; Hauser, R. Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. *Sci. Total Environ.* **2009**, *407* (10), 3425-3429.
10. Abdelouahab, N.; Ainmelk, Y.; Takser, L. Polybrominated diphenyl ethers and sperm quality. *Reprod. Toxicol.* **2011**, *31* (4), 546-550.
11. Herbstman, J. B.; Sjödin, A.; Kurzon, M.; Lederman, S. A.; Jones, R. S.; Rauh, V.; Needham, L. L.; Tang, D.; Niedzwiecki, M.; Wang, R. Y.; Perera, F. Prenatal exposure to PBDEs and neurodevelopment. *Environ. Health Perspect.* **2010**, *118* (5), 712-719.
12. Chao, H. R.; Tsou, T. C.; Huang, H. L.; Chang-Chien, G. P. Levels of breast milk PBDEs from Southern Taiwan and their potential impact on neurodevelopment. *Pediatr. Res.* **2011**, *70* (6), 596-600.
13. Chen, A.; Yolton, K.; Rauch, S. A.; Webster, G. M.; Hornung, R.; Sjödin, A.; Dietrich, K. N.; Lanphear, B. P. Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: the HOME study. *Environ. Health Perspect.* **2014**, *122* (8), 856-862.
14. Herbstman, J. B.; Mall, J. K. Developmental exposure to polybrominated diphenyl ethers and neurodevelopment. *Curr. Environ. Health Rep.* **2014**, *1* (2), 101-112.

15. Chevrier, C.; Warembourg, C.; Le Maner-Idrissi, G.; Lacroix, A.; Dardier, V.; Le Sourn-Bissaoui, S.; Rouget, F.; Monfort, C.; Gaudreau, E.; Mercier, F.; Bonvallot, N.; Glorennec, P.; Muckle, G.; Le Bot, B.; Cordier, S. Childhood exposure to polybrominated diphenyl ethers and neurodevelopment at six years of age. *Neurotoxicology* **2016**, *54*, 81-88.
16. Zhang, H.; Yolton, K.; Webster, G. M.; Sjodin, A.; Calafat, A. M.; Dietrich, K. N.; Xu, Y.; Xie, C.; Braun, J. M.; Lanphear, B. P.; Chen, A. Prenatal PBDE and PCB exposures and reading, cognition, and externalizing behavior in children. *Environ. Health Perspect.* **2016**, epub ahead of print.
17. Besis, A.; Samara, C. Polybrominated diphenyl ethers (PBDEs) in the indoor and outdoor environments – a review on occurrence and human exposure. *Environ. Pollut.* **2012**, *169*, 217-229.
18. Johnson-Restrepo, B.; Kannan, K. An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere.* **2009**, *76* (4), 542-548.
19. Schecter, A.; Päpke, O.; Joseph, J. E.; Tung, K. C. Polybrominated diphenyl ethers (PBDEs) in U.S. computers and domestic carpet vacuuming: possible sources of human exposure. *J. Toxicol. Environ. Health A.* **2005**, *68* (7), 501-513.
20. Harrad, S.; Ibarra, C.; Diamond, M.; Melymuk, L.; Robson, M.; Douwes, J.; Roosens, L.; Dirtu, A. C.; Covaci, A. Polybrominated diphenyl ethers in domestic indoor dust from Canada, New Zealand, United Kingdom and United States. *Environ. Int.* **2008**, *34* (2), 232-238.
21. Fraser, A. J.; Webster, T. F.; McClean, M. D. Diet contributes significantly to the body burden of PBDEs in the general U.S. population. *Environ. Health Perspect.* **2009**, *117* (10), 1520-1525.
22. Ni, H. G.; Ding, C.; Lu, S. Y.; Yin, X. L.; Samuel, S. O. Food as a main route of adult exposure to PBDEs in Shenzhen, China. *Sci. Total Environ.* **2012**, *437*, 10-14.
23. van der Veen, I.; de Boer, J. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere.* **2012**, *88* (10), 1119-1153.
24. Hartmann, P. C.; Bürgi, D.; Giger, W. Organophosphate flame retardants and plasticizers in indoor air. *Chemosphere.* **2004**, *57* (8), 781-787.
25. Dodson, R. E.; Perovich, L. J.; Covaci, A.; Van den Eede, N.; Ionas, A. C.; Dirtu, A. C.; Brody, J. G.; Rudel, R. A. After the PBDE phase-out: a broad suite of flame retardants in repeat house dust samples from California. *Environ. Sci. Technol.* **2012**, *46* (24), 13056-13066.
26. Liu, X.; Ji, K.; Choi, K. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. *Aquat. Toxicol.* **2012**, *114-115*, 173-181.
27. Chen, G.; Jin, Y.; Wu, Y.; Liu, L.; Fu, Z. Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. *Environ. Toxicol. Pharmacol.* **2015**, *40* (1), 310-318.
28. CA EPA. Chemicals known to the state to cause cancer or reproductive toxicity. California Environmental Protection Agency, Sacramento, CA, Office of Environmental Health Hazard Assessment, **2017**.
29. Muenhor, D.; Harrad, S.; Ali, N.; Covaci, A. Brominated flame retardants (BFRs) in air and dust from electronic waste storage facilities in Thailand. *Environ. Int.* **2010**, *36* (7), 690-698.

30. Watkins, D. J.; McClean, M. D.; Fraser, A. J.; Weinberg, J.; Stapleton, H. M.; Sjödin, A.; Webster, T. F. Exposure to PBDEs in the office environment: evaluating the relationships between dust, handwipes, and serum. *Environ. Health Perspect.* **2011**, *119* (9), 1247-1252.
31. He, C. T.; Zheng, J.; Qiao, L.; Chen, S. J.; Yang, J. Z.; Yuan, J. G.; Yang, Z. Y.; Mai, B. X. Occurrence of organophosphorus flame retardants in indoor dust in multiple microenvironments of southern China and implications for human exposure. *Chemosphere.* **2015**, *133*, 47-52.
32. Shen, B.; Whitehead, T. P.; McNeel, S.; Brown, F. R.; Dhaliwal, J.; Das, R.; Israel, L.; Park, J. S.; Petreas, M. High levels of polybrominated diphenyl ethers in vacuum cleaner dust from california fire stations. *Environ. Sci. Technol.* **2015**, *49* (8), 4988-4994.
33. Shaw, S. D.; Berger, M. L.; Harris, J. H.; Yun, S. H.; Wu, Q.; Liao, C.; Blum, A.; Stefani, A.; Kannan, K. Persistent organic pollutants including polychlorinated and polybrominated dibenzo-p-dioxins and dibenzofurans in firefighters from Northern California. *Chemosphere.* **2013**, *91* (10), 1386-1394.
34. Park, J. S.; Voss, R. W.; McNeel, S.; Wu, N.; Tan, G.; Wang, Y.; Israel, L.; Das, R.; Petreas, M. High exposure of California firefighters to polybrominated diphenyl ethers. *Environ. Sci. Technol.* **2015**, *49* (5), 2948-2958.
35. Walton, S. M.; Conrad, K. M.; Furner, S. E.; Samo, D. G. Cause, type, and workers' compensation costs of injury to fire fighters. *Am. J. Ind. Med.* **2003**, *43* (4), 454-458.
36. Chiou, S. S.; Turner, N.; Zwiener, J.; Weaver, D. L.; Haskell, W. E. Effect of boot weight and sole flexibility on gait and physiological responses of firefighters in stepping over obstacles. *Hum. Factors.* **2012**, *54* (3), 373-386.
37. Plat, M. C.; Frings-Dresen, M. H.; Sluiter, J. K. Diminished health status in firefighters. *Ergonomics.* **2012**, *55* (9), 1119-1122.
38. Berninger, A.; Webber, M. P.; Niles, J. K.; Gustave, J.; Lee, R.; Cohen, H. W.; Kelly, K.; Corrigan, M.; Prezant, D. J. Longitudinal study of probable post-traumatic stress disorder in firefighters exposed to the World Trade Center disaster. *Am. J. Ind Med.* **2010**, *53* (12), 1177-1185.
39. Webber, M. P.; Glaser, M. S.; Weakley, J.; Soo, J.; Ye, F.; Zeig-Owens, R.; Weiden, M. D.; Nolan, A.; Aldrich, T. K.; Kelly, K.; Prezant, D. Physician-diagnosed respiratory conditions and mental health symptoms seven to nine years following the World Trade Center disaster. *Am. J. Ind. Med.* **2011**, *54* (9), 661-671.
40. Fushimi, M. Posttraumatic stress in professional firefighters in Japan: rescue efforts after the Great East Japan Earthquake (Higashi Nihon Dai-Shinsai). *Prehosp. Disaster Med.* **2012**, *27* (5), 416-418.
41. Jankovic, J.; Jones, W.; Burkhart, J.; Noonan, G. Environmental study of firefighters. *Ann. Occup. Hyg.* **1991**, *35* (6), 581-602.
42. McDiarmid, M. A.; Lees, P. S.; Agnew, J.; Midzenski, M.; Duffy, R. Reproductive hazards of fire fighting. II. Chemical hazards. *Am. J. Ind. Med.* **1991**, *19* (4), 447-472.
43. Fent, K. W.; Evans, D. E. Assessing the risk to firefighters from chemical vapors and gases during vehicle fire suppression. *J. Environ. Monit.* **2011**, *13* (3), 536-543.
44. Laitinen, J.; Makela, M.; Mikkola, J.; Huttu, I. Firefighters' multiple exposure assessments in practice. *Toxicol. Lett.* **2012**, *213* (1), 129-133.
45. McNamara, M. L.; Semmens, E. O.; Gaskill, S.; Palmer, C.; Noonan, C. W.; Ward, T. J. Base camp personnel exposure to particulate matter during wildland fire suppression activities. *J. Occup. Environ. Hyg.* **2012**, *9* (3), 149-156.

46. Fent, K. W.; Eisenberg, J.; Snawder, J.; Sammons, D.; Pleil, J. D.; Stiegel, M. A.; Mueller, C.; Horn, G. P.; Dalton, J. Systemic exposure to PAHs and benzene in firefighters suppressing controlled structure fires. *Ann. Occup. Hyg.* **2014**, *58* (7), 830-845.
47. Evans, D. E.; Fent, K. W. Ultrafine and respirable particle exposure during vehicle fire suppression. *Environ. Sci. Process. Impacts.* **2015**, *17* (10), 1749-1759.
48. Wobst, M.; Wichmann, H.; Bahadir, M. Surface contamination with PASH, PAH and PCDD/F after fire accidents in private residences. *Chemosphere.* **1999**, *38* (7), 1685-1691.
49. Bolstad-Johnson, D. M.; Burgess, J. L.; Crutchfield, C. D.; Storment, S.; Gerkin, R.; Wilson, J. R. Characterization of firefighter exposures during fire overhaul. *AIHAJ.* **2000**, *61* (5), 636-641.
50. Burgess, J. L.; Nanson, C. J.; Bolstad-Johnson, D. M.; Gerkin, R.; Hysong, T. A.; Lantz, R. C.; Sherrill, D. L.; Crutchfield, C. D.; Quan, S. F.; Bernard, A. M.; Witten, M. L. Adverse respiratory effects following overhaul in firefighters. *J. Occup. Environ. Med.* **2001**, *43* (5), 467-473.
51. Baxter, C. S.; Hoffman, J. D.; Knipp, M. J.; Reponen, T.; Haynes, E. N. Exposure of firefighters to particulates and polycyclic aromatic hydrocarbons. *J. Occup. Environ. Hyg.* **2014**, *11* (7), D85-D91.
52. Daniels, R. D.; Bertke, S.; Dahm, M. M.; Yiin, J. H.; Kubale, T. L.; Hales, T. R.; Baris, D.; Zahm, S. H.; Beaumont, J. J.; Waters, K. M.; Pinkerton, L. E. Exposure–response relationships for select cancer and non-cancer health outcomes in a cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950–2009). *Occup. Environ. Med.* **2015**, *72* (10), 699-706.
53. Bates, M. N.; Fawcett, J.; Garrett, N.; Arnold, R.; Pearce, N.; Woodward, A. Is testicular cancer an occupational disease of fire fighters? *Am. J. Ind. Med.* **2001**, *40* (3), 263-270.
54. LeMasters, G. K.; Genaidy, A. M.; Succop, P.; Deddens, J.; Sobeih, T.; Barriera-Viruet, H.; Dunning, K.; Lockey, J. Cancer risk among firefighters: a review and meta-analysis of 32 studies. *J. Occup. Environ. Med.* **2006**, *48* (11), 1189-1202.
55. Bates, M. N. Registry-based case–control study of cancer in California firefighters. *Am. J. Ind. Med.* **2007**, *50* (5), 339-344.
56. Daniels, R. D.; Kubale, T. L.; Yiin, J. H.; Dahm, M. M.; Hales, T. R.; Baris, D.; Zahm, S. H.; Beaumont, J. J.; Waters, K. M.; Pinkerton, L. E. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950–2009). *Occup. Environ. Med.* **2014**, *71* (6), 388-397.
57. Schottenfeld, D.; Fraumeni Jr., J. F. *Cancer epidemiology and prevention*. Oxford University Press: **2006**, 3rd ed.
58. U. S. EPA. TSCA Chemical Substance Inventory. **2015**.
59. Wilson, M. P. & Schwarzman, M. R. Toward a new U.S. chemicals policy: rebuilding the foundation to advance new science, green chemistry, and environmental health. *Environ. Health Perspect.* **2009**, *117* (8), 1202-1209.
60. Schwarzman, M. R. & Wilson, M. P. Science and regulation. New science for chemicals policy. *Science.* **2009**, *326* (5956), 1065-1066.
61. Trasande, L. Updating the Toxic Substances Control Act to protect human health. *JAMA.* **2016**, *315* (15), 1565-1566.
62. U. S. EPA. Chemical safety for sustainability: strategic research action plan 2016-2019. U. S. Environmental Protection Agency, Office of Research and Development, **2015**.
63. U. S. EPA. Polybrominated Diphenyl Ethers (PBDEs) Action Plan. **2009**.

64. Hauschild, M. Z. Assessing environmental impacts in a life-cycle perspective. *Environ. Sci. Technol.* **2005**, *39* (4), 81A-88A.
65. Hellweg, S.; Milà i Canals, L. Emerging approaches, challenges and opportunities in life cycle assessment. *Science.* **2014**, *344* (6188), 1109-1113.
66. Hellweg, S.; Demou, E.; Bruzzi, R.; Meijer, A.; Rosenbaum, R. K.; Huijbregts, M. A. J.; McKone, T. E. Integrating human indoor air pollutant exposure within life cycle impact assessment. *Environ. Sci. Technol.* **2009**, *43* (6), 1670-1679.
67. Kijko, G.; Margni, M.; Partovi-Nia, V.; Doudrich, G.; Jolliet, O. Impact of occupational exposure to chemicals in life cycle assessment: a novel characterization model based on measured concentrations and labor hours. *Environ. Sci. Technol.* **2015**, *49* (14), 8741-8750.
68. Hellweg, S.; Demou, E.; Scheringer, M.; McKone, T.; Hungerbuehler, K. Confronting workplace exposure to chemicals with LCA: the examples of trichloroethylene and tetrachloroethylene in metal-degreasing and dry-cleaning. *Environ. Sci. Technol.* **2005**, *39* (19), 7741-7748.
69. Demou, E.; Hellweg, S.; Wilson, M. P.; Hammond, S. K.; McKone, T. E. Evaluating indoor exposure modeling alternatives for LCA: a case study in the vehicle repair industry. *Environ. Sci. Technol.* **2009**, *43* (15), 5804-5810.
70. Lorber, M. Exposure of Americans to polybrominated diphenyl ethers. *J. Expo. Sci. Environ. Epidemiol.* **2008**, *18* (1), 2-19.
71. Stapleton, H. M.; Sharma, S.; Getzinger, G.; Ferguson, P. L.; Gabriel, M.; Webster, T. F.; Blum, A. Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. *Environ. Sci Technol.* **2012**, *46* (24), 13432-13439.
72. ATSDR. Toxicological profile for phosphate ester flamer retardants. U. S. Department of Human Health and Services. **2012**.
73. Sjödin, A.; Carlsson, H.; Thuresson, K.; Sjölin, S.; Bergman, A.; Ostman, C. Flame retardants in indoor air at an electronics recycling plant and at other work environments. *Environ. Sci. Technol.* **2001**, *35* (3), 448-454.
74. Bradman, A.; Castorina, R.; Gaspar, F.; Nishioka, M.; Colón, M.; Weathers, W.; Egeghy, P. P.; Maddalena, R.; Williams, J.; Jenkins, P. L.; McKone, T. E. Flame retardant exposures in California early childhood education environments. *Chemosphere.* **2014**, *116*, 61-66.
75. Stapleton, H. M.; Klosterhaus, S.; Eagle, S.; Fuh, J.; Meeker, J. D.; Blum, A.; Webster, T. F. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. *Environ. Sci. Technol.* **2009**, *43* (19), 7490-7495.
76. Horn, G.; Kerber, S.; Fent, K.; Fernhall, B.; Smith, D. Cardiovascular & chemical exposure risks in modern firefighting: interim report. Illinois Fire Service Report. **2016**.
77. Jayatilaka, N. K.; Restrepo, P.; Williams, L.; Ospina, M.; Valentin-Blasini, L.; Calafat, A. M. Quantification of three chlorinated dialkyl phosphates, diphenyl phosphate, 2,3,4,5-tetrabromobenzoic acid, and four other organophosphates in human urine by solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. *Anal. Bioanal. Chem.* **2017**, *409* (5), 1323-1332.
78. Brown, F. R.; Whitehead, T. P.; Park, J. S.; Metayer, C.; Petreas, M. X. Levels of non-polybrominated diphenyl ether brominated flame retardants in residential house dust samples and fire station dust samples in California. *Environ. Res.* **2014**, *135*, 9-14.
79. Zota, A. R.; Rudel, R. A.; Morello-Frosch, R. A.; Brody, J. G. Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? *Environ. Sci. Technol.* **2008**, *42* (21), 8158-8164.

80. Van den Eede, N.; Dirtu, A. C.; Ali, N.; Neels, H.; Covaci, A. Multi-residue method for the determination of brominated and organophosphate flame retardants in indoor dust. *Talanta*. **2012**, *89*, 292-300.
81. CA EPA. Standard Operating Procedure - Determination of organophosphate and brominated flame retardants in house dust and consumer products by gas chromatography-tandem mass spectrometry. Department of Toxic Substances Control, Berkeley, CA, DCN: 05.0029.00, **2017**.
82. Whitehead, T. P.; Brown, F. R.; Metayer, C.; Park, J. S.; Does, M.; Petreas, M. X.; Buffler, P. A.; Rappaport, S. M. Polybrominated diphenyl ethers in residential dust: sources of variability. *Environ. Int.* **2013**, *57-58*, 11-24.
83. Whitehead, T.; Metayer, C.; Buffler, P.; Rappaport, S. M. Estimating exposures to indoor contaminants using residential dust. *J. Expo. Sci. Environ. Epidemiol.* **2011**, *21* (6), 549-564.
84. Alaee, M.; Arias, P.; Sjödin, A.; Bergman, A. An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. *Environ. Int.* **2003**, *29* (6), 683-689.
85. Van den Eede, N.; Dirtu, A. C.; Neels, H.; Covaci, A. Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust. *Environ. Int.* **2011**, *37* (2), 454-461.
86. Stapleton, H. M.; Allen, J. G.; Kelly, S. M.; Konstantinov, A.; Klosterhaus, S.; Watkins, D.; McClean, M. D.; Webster, T. F. Alternate and new brominated flame retardants detected in U.S. house dust. *Environ. Sci. Technol.* **2008**, *42* (18), 6910-6916.
87. U. S. EPA. Exposure Factors Handbook 2011 Edition (Final). U. S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, **2011**.
88. U. S. EPA. 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209); CASRN 1163-19-5 Chemical Assessment Summary. U. S. Environmental Protection Agency, Washington, DC, Integrated Risk Information System (IRIS), **2008**.
89. Brommer, S.; Harrad, S. Sources and human exposure implications of concentrations of organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices. *Environ. Int.* **2015**, *83*, 202-207.
90. Dodson, R. E.; Rodgers, K. M.; Carey, G.; Cedeno Laurent, J. G.; Covaci, A.; Poma, G.; Malarvannan, G.; Spengler, J. D.; Rudel, R. A.; Allen, J. G. Flame retardant chemicals in college dormitories: flammability standards influence dust concentrations. *Environ. Sci. Technol.* **2017**, *51* (9), 4860-4869.
91. Hoffman, K.; Garantziotis, S.; Birnbaum, L. S.; Stapleton, H. M. Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. *Environ. Health Perspect.* **2015**, *123* (2), 160-165.
92. Mizouchi, S.; Ichiba, M.; Takigami, H.; Kajiwara, N.; Takamuku, T.; Miyajima, T.; Kodama, H.; Someya, T.; Ueno, D. Exposure assessment of organophosphorus and organobromine flame retardants via indoor dust from elementary schools and domestic houses. *Chemosphere.* **2015**, *123*, 17-25.
93. Alexander, B. M. & Baxter, C. S. Flame-retardant contamination of firefighter personal protective clothing - a potential health risk for firefighters. *J. Occup. Environ. Hyg.* **2016**, *13* (9), D148-D155.
94. Easter, E.; Lander, D.; Huston, T. Risk assessment of soils identified on firefighter turnout gear. *J. Occup. Environ. Hyg.* **2016**, *13* (9), 647-657.

95. de Perio, M. A.; Durgam, S.; Caldwell, K. L.; Eisenberg, J. A health hazard evaluation of antimony exposure in fire fighters. *J. Occup. Environ. Med.* **2010**, *52* (1), 81-84.
96. Curl, C. L.; Fenske, R. A.; Kissel, J. C.; Shirai, J. H.; Moate, T. F.; Griffith, W.; Coronado, G.; Thompson, B. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environ. Health Perspect.* **2002**, *110* (12), A787-A792.
97. Coronado, G. D.; Vigoren, E. M.; Thompson, B.; Griffith, W. C.; Faustman, E. M. Organophosphate pesticide exposure and work in pome fruit: evidence for the take-home pesticide pathway. *Environ. Health Perspect.* **2006**, *114* (7), 999-1006.
98. Suarez-Lopez, J. R.; Jacobs, D. R. Jr.; Himes, J. H.; Alexander, B. H.; Lazovich, D.; Gunnar, M. Lower acetylcholinesterase activity among children living with flower plantation workers. *Environ. Res.* **2012**, *114*, 53-59.
99. Allen, J. G.; McClean, M. D.; Stapleton, H. M.; Webster, T. F. Linking PBDEs in house dust to consumer products using x-ray fluorescence. *Environ. Sci. Technol.* **2008**, *42* (11), 4222-4228.
100. Yang, F.; Ding, J.; Huang, W.; Xie, W.; Liu, W. Particle size-specific distributions and preliminary exposure assessments of organophosphate flame retardants in office air particulate matter. *Environ. Sci. Technol.* **2014**, *48* (1), 63-70.
101. Zhou, L.; Hiltscher, M.; Gruber, D.; Püttmann, W. Organophosphate flame retardants (OPFRs) in indoor and outdoor air in the Rhine/Main area, Germany: comparison of concentrations and distribution profiles in different microenvironments. *Environ. Sci. Pollut. Res.* **2017**, *24* (12), 10992-11005.
102. Shen, B.; Whitehead, T. P.; Gill, R.; Dhaliwal, J.; Brown, F. R.; Petreas, M.; Patton, S.; Hammond, S. K. Organophosphate flame retardants in dust collected from United States fire stations. *Environ. Int.* **2018**, *112*, 41-48.
103. Bollmann, U. E.; Möller, A.; Xie, Z.; Ebinghaus, R.; Einax, J. W. Occurrence and fate of organophosphorus flame retardants and plasticizers in coastal and marine surface waters. *Water Res.* **2012**, *46* (2), 531–538.
104. Hu, M.; Li, J.; Zhang, B.; Cui, Q.; Wei, S.; Yu, H. Regional distribution of halogenated organophosphate flame retardants in seawater samples from three coastal cities in China. *Mar. Pollut. Bull.* **2014**, *86* (1-2), 569-574.
105. Zhong, M.; Tang, J.; Mi, L.; Li, F.; Wang, R.; Huang, G.; Wu, H. Occurrence and spatial distribution of organophosphorus flame retardants and plasticizers in the Bohai and Yellow Seas, China. *Mar. Pollut. Bull.* **2017**, *121* (1-2), 331-338.
106. Giulivo, M.; Capri, E.; Kalogianni, E.; Milacic, R.; Majone, B.; Ferrari, F.; Eljarrat, E.; Barceló, D. Occurrence of halogenated and organophosphate flame retardants in sediment and fish samples from three European river basins. *Sci. Total Environ.* **2017**, *586*, 782-791.
107. Lee, S.; Cho, H. J.; Choi, W.; Moon, H. B. Organophosphate flame retardants (OPFRs) in water and sediment: occurrence, distribution, and hotspots of contamination of Lake Shihwa, Korea. *Mar. Pollut. Bull.* **2018**, *130*, 105-112.
108. Turyk M. E.; Persky, V. W.; Imm, P.; Knobeloch, L.; Chatterton, R.; Anderson, H. A. Hormone disruption by PBDEs in adult male sport fish consumers. *Environ. Health Perspect.* **2008**, *116* (12), 1635-1641.
109. Eskenazi, B.; Rauch, S. A.; Tenerelli, R.; Huen, K.; Holland, N. T.; Lustig, R. H.; Kogut, K.; Bradman, A.; Sjödin, A.; Harley, K. G. In utero and childhood DDT, DDE, PBDE and

PCBs exposure and sex hormones in adolescent boys: The CHAMACOS study. *Int. J. Hyg. Environ. Health.* **2017**, *220* (2 Pt B), 364-372.
110. Johnson, P. I.; Stapleton, H. M.; Mukherjee, B.; Hauser, R.; Meeker, J. D. Associations between brominated flame retardants in house dust and hormone levels in men. *Sci. Total Environ.* **2013**, *445–446*, 177-184.
111. Krivoshiev, B. V.; Dardenne, F.; Covaci, A.; Blust, R.; Husson, S. J. Assessing in-vitro estrogenic effects of currently-used flame retardants. *Toxicol. In Vitro.* **2016**, *33*, 153-162.
112. Zhang, Q.; Lu, M.; Dong, X.; Wang, C.; Zhang, C.; Liu, W.; Zhao, M. Potential estrogenic effects of phosphorus-containing flame retardants. *Environ. Sci. Technol.* **2014**, *48* (12), 6995-7001.
113. Zhang, Q.; Ji, C.; Yin, X.; Yan, L.; Lu, M.; Zhao, M. Thyroid hormone-disrupting activity and ecological risk assessment of phosphorus-containing flame retardants by in vitro, in vivo and in silico approaches. *Environ. Pollut.* **2016**, *210*, 27-33.
114. Kojima, H.; Takeuchi, S.; Itoh, T.; Iida, M.; Kobayashi, S.; Yoshida, T. In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors. *Toxicology.* **2013**, *314* (1), 76-83.
115. Du, Z.; Zhang, Y.; Wang, G.; Peng, J.; Wang, Z.; Gao, S. TPhP exposure disturbs carbohydrate metabolism, lipid metabolism, and the DNA damage repair system in zebrafish liver. *Sci. Rep.* **2016**, *6*, 218-227.
116. Mendelsohn, E.; Hagopian, A.; Hoffman, K.; Butt, C. M.; Lorenzo, A.; Congleton, J.; Webster, T. F.; Stapleton, H. M. Nail polish as a source of exposure to triphenyl phosphate. *Environ. Int.* **2016**, *86*, 45-5.
117. Meeker, J. D.; Stapleton, H. M. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. *Environ. Health Perspect.* **2010**, *118* (3), 318-323.
118. Eskenazi, B. *et al.* Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Env. Health Perspect* **112**, 1116–24 (2004).
119. Eskenazi, B.; Marks, A. R.; Bradman, A.; Fenster, L.; Johnson, C.; Barr, D. B.; Jewell, N. P. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. *Pediatrics.* **2006**, *118* (1), 233-241.
120. Castorina, R.; Butt, C.; Stapleton, H. M.; Avery, D.; Harley, K. G.; Holland, N.; Eskenazi, B.; Bradman, A. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). *Chemosphere*. **2017**, *179*, 159-166.
121. Butt, C. M.; Congleton, J.; Hoffman, K.; Fang, M.; Stapleton, H. M. Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. *Environ. Sci. Technol.* **2014**, *48* (17), 10432-10438.
122. Soldin, O. P.; Hoffman, E. G.; Waring, M. A.; Soldin, S. J. Pediatric reference intervals for FSH, LH, estradiol, T3, free T3, cortisol, and growth hormone on the DPC IMMULITE 1000. *Clin. Chim. Acta.* **2005**, *355* (1-2), 205-210.
123. Vesper, H. W.; Wang, Y.; Vidal, M.; Botelho, J. C.; Caudill, S. P. Serum total testosterone concentrations in the US household population from the NHANES 2011-2012 study population. *Clin. Chem.* **2015**, *61* (12), 1495-1504.

124. FSH | Medical Tests | UCSF Benioff Children's Hospital. https://www.ucsfbenioffchildrens.org/tests/003710.html. Accessed September 25, 2019.
125. Castorina, R.; Bradman, A.; Stapleton, H. M.; Butt, C.; Avery, D.; Harley, K. G.; Gunier, R. B.; Holland, N.; Eskenazi, B. Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. *Chemosphere.* **2017**, *189*, 574-580.
126. Hoffman, K.; Daniels, J. L.; Stapleton, H. M. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. *Environ. Int.* **2014**, *63*, 169-172.
127. Meeker, J. D.; Godfrey-Bailey, L.; Hauser, R. Relationships between serum hormone levels and semen quality among men from an infertility clinic. *J. Androl.* **2007**, *28* (3), 397-406.
128. Gordetsky, J.; van Wijngaarden, E.; O'Brien, J. Redefining abnormal follicle-stimulating hormone in the male infertility population. *BJU Int.* **2012**, *110* (4), 568-572.
129. Dickerman, Z.; Bar-Haim, Y.; Prager-Lewin, R.; Kaufman, H.; Laron, Z. Plasma LH and FSH response to LRH and plasma testosterone levels in boys with irregular puberty. *Eur. J. Endocrinol.* **1977**, *85* (3), 456-464.
130. Dishaw, L. V.; Macaulay, L. J.; Roberts, S. C.; Stapleton, H. M. Exposures, mechanisms, and impacts of endocrine-active flame retardants. *Curr. Opin. Pharmacol.* **2014**, 19, 125-133.
131. Khan, S. & Malik, A. Environmental Deterioration and Human Health: Natural and anthropogenic determinants. *Environmental and health effects of textile industry wastewater*. **2014**, 55-71.
132. Nimkar, U. Sustainable chemistry: A solution to the textile industry in a developing world. *Curr. Opin. Green Sustain. Chem.* **2018**, *9*, 13-17.
133. Checkoway, H.; Ray, R. M.; Lundin, J. I.; Astrakianakis, G.; Seixas, N. S.; Camp, J. E.; Wernli, K. J.; Fitzgibbons, E. D.; Li, W.; Feng, Z.; Gao, D. L.; Thomas, D. B. Lung cancer and occupational exposures other than cotton dust and endotoxin among women textile workers in Shanghai, China. *Occup. Environ. Med.* **2011**, *68* (6), 425-429.
134. Li, W.; Ray, R. M.; Gao, D. L.; Fitzgibbons, E. D.; Seixas, N. S.; Camp, J. E.; Wernli, K. J.; Astrakianakis, G.; Feng, Z.; Thomas, D. B.; Checkoway, H. Occupational risk factors for nasopharyngeal cancer among female textile workers in Shanghai, China. *Occup. Environ. Med.* **2006**, *63* (1), 39-44.
135. Lindbohm, M. L., Hemminki, K.; Kyyrönen, P. Parental occupational exposure and spontaneous abortions in Finland. *Am. J. Epidemiol.* **1984**, *120* (3), 370-378.
136. Colt, J. S. & Blair, A. Parental occupational exposures and risk of childhood cancer. *Environ. Health Perspect.* **1998**, *106* (3), 909-925.
137. Greenpeace. Dirty Laundry: Unravelling the corporate connections to toxic water pollution in China. **2011**.
138. H&M. https://www2.hm.com/en_us/women/campaigns/16r-garment-collecting.html. Accessed October 17, 2019.
139. Levi's®. http://store.levi.com/waterless/. Accessed October 17, 2019.
140. Hilty, L. M. Electronic waste – an emerging risk? *Environ. Impact Assess. Rev.* **2005**, *25* (5), 431-435.
141. Widmer, R.; Oswald-Krapf, H.; Sinha-Khetriwal, D.; Schnellmann, M.; Böni, H. Global perspectives on e-waste. *Environ. Impact Assess. Rev.* **2005**, *25* (5), 436-458.
142. Geiser, K. Health hazards in the microelectronics industry. *Int. J. Health Serv.* **1986**, *16* (1), 105-120.

143. Koh, D.; Chan, G.; Yap, E. World at work: the electronics industry. *Occup. Environ. Med.* **2004**, *61*, 180-183.
144. Lécuyer, C. From clean rooms to dirty water: labor, semiconductor firms, and the struggle over pollution and workplace hazards in Silicon Valley. *Inf. Cult.* **2017**, *52* (3), 304-333.
145. Logsdon, J. M. Collaboration to regulate L.U.S.T.: leaking underground storage tanks in Silicon Valley. *J. Bus. Res.* **1991**, *23* (1), 99-111.
146. Deane, M.; Swan, S. H.; Harris, J. A.; Epstein, D. M.; Neutra, R. R. Adverse pregnancy outcomes in relation to water contamination, Santa Clara County, California, 1980-1981. *Am. J. Epidemiol.* **1989**, *129* (5), 894-904.
147. Swan, S. H.; Shaw, G.; Harris, J. A.; Neutra, R. R. Congenital cardiac anomalies in relation to water contamination, Santa Clara County, California, 1981-1983. *Am. J. Epidemiol.* **1989**, *129* (5), 885-893.
148. Olivieri, A.; Eisenberg, D.; Kurtovich, M.; Pettegrew, L. Ground-water contamination in Silicon Valley. *J. Water Resour. Plan. Manag.* **1985**, *111* (3), 346-358.
149. U. S. EPA. What is Superfund? **2017**.
150. U. S. EPA. Superfund Sites in Reuse in California. **2016**.
151. LaDou, J. Potential occupational health hazards in the microelectronics industry. *Scand. J. Work. Environ. Health* **1983**, *9* (1), 42-46.
152. Edelman, P. Environmental and workplace contamination in the semiconductor industry: implications for future health of the workforce and community. *Environ. Health Perspect.* **1990**, *86*, 291-295.
153. Woskie, S. R.; Hammond, S. K.; Hines, C. J.; Hallock, M. F.; Kenyon, E.; Schenker, M. B. Personal fluoride and solvent exposures, and their determinants, in semiconductor manufacturing. *Appl. Occup. Environ. Hyg.* **2000**, *15* (4), 354-361.
154. Beaumont, J. J.; Swan, S. H.; Hammond, S. K.; Samuels, S. J.; Green R. S.; Hallock, M. F.; Dominguez, C.; Boyd, P.; Schenker, M. B. Historical cohort investigation of spontaneous abortion in the Semiconductor Health Study: epidemiologic methods and analyses of risk in fabrication overall and in fabrication work groups. *Am. J. Ind. Med.* **1995**, *28* (6), 735-750.
155. Eskenazi, B.; Gold, E. B.; Lasley, B. L.; Samuels, S. J.; Hammond, S. K.; Wight, S.; O'Neill Rasor, M.; Hines, C. J.; Schenker, M. B. Prospective monitoring of early fetal loss and clinical spontaneous abortion among female semiconductor workers. *Am. J. Ind. Med.* **1995**, *28* (6), 833-846.
156. Gold, E. B.; Eskenazi, B.; Hammond, S. K.; Lasley, B. L.; Samuels, S. J.; O'Neill Rasor, M.; Hines, C. J.; Overstreet, J. W.; Schenker, M. B. Prospectively assessed menstrual cycle characteristics in female wafer-fabrication and nonfabrication semiconductor employees. *Am. J. Ind. Med.* **1995**, *28* (6), 799-815.
157. Chang, Y. M.; Tai, C. F.; Lin, R. S.; Yang, S. C.; Chen, C. J.; Shih, T. S.; Liou, S. H. A proportionate cancer morbidity ratio study of workers exposed to chlorinated organic solvents in Taiwan. *Ind. Health.* **2003**, *41* (2), 77-87.
158. Hsieh, G. Y.; Wang, J. D.; Cheng, T. J.; Chen, P. C. Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry. *Occup. Environ. Med.* **2005**, *62* (8), 510-516.
159. Sung, T. I.; Wang, J. D.; Chen, P. C. Increased risks of infant mortality and of deaths due to congenital malformation in the offspring of male electronics workers. *Birth Defects Res. A. Clin. Mol. Teratol.* **2009**, *85* (2), 119-124.

160. Kim, E. A.; Lee, H. E.; Ryu, H. W.; Park, S. H.; Kang, S. K. Cases series of malignant lymphohematopoietic disorder in Korean semiconductor industry. *Saf. Health Work.* **2011**, *2* (2), 122-134.
161. Lee, H. E.; Kim, E. A.; Park, J.; Kang, S. K. Cancer mortality and incidence in Korean semiconductor workers. *Saf. Health Work.* **2011**, *2* (2), 135-147.
162. Kim, I.; Kim, H. J.; Lim, S. Y.; Kongyoo, J. Leukemia and non-Hodgkin lymphoma in semiconductor industry workers in Korea. *Int. J. Occup. Environ. Health.* **2012**, *18* (2), 147-153.
163. Park, D. U.; Choi, S.; Lee, S.; Koh, D. H.; Kim, H. R.; Lee, K. H.; Park, J. Occupational characteristics of semiconductor workers with cancer and rare diseases registered with a workers' compensation program in Korea. *Saf. Health Work.* **2019**, *10* (3), 347-354.
164. Vågerö, D. & Olin, R. Incidence of cancer in the electronics industry: using the new Swedish Cancer Environment Registry as a screening instrument. *Occup. Environ. Med.* **1983**, *40* (2), 188-192.
165. Sorahan, T.; Waterhouse, J. A.; McKiernan, M. J.; Aston, R. H. Cancer incidence and cancer mortality in a cohort of semiconductor workers. *Occup. Environ. Med.* **1985**, *42* (8), 546-550.
166. Elliott, R. C.; Jones, J. R.; McElvenny, D. M.; Pennington, M. J.; Northage, C.; Clegg, T. A.; Clarke, S. D.; Hodgson, J. T.; Osman, J. Spontaneous abortion in the British semiconductor industry: An HSE investigation. Health and Safety Executive. *Am. J. Ind. Med.* **1999**, *36* (5), 557-572.
167. McElvenny, D. M.; Darnton, A. J.; Hodgson, J. T.; Clarke, S. D.; Elliott, R. C.; Osman, J. Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility. *Occup. Med.* **2003**, *53* (7), 419-430.
168. Kim, M. H., Kim, H.; Paek, D. The health impacts of semiconductor production: an epidemiologic review. *Int. J. Occup. Environ. Health.* **2014**, *20* (2), 95-114.
169. NPR. Samsung Apologizes To Ill Workers, Promises To Compensate Them. https://www.npr.org/2018/11/23/670429271/samsung-apologizes-to-ill-workers-promises-to-compensate-them. Accessed October 17, 2019.
170. Lee, M. & Waitzkin, H. A heroic struggle to understand the risk of cancers among workers in the electronics industry: the case of Samsung. *Int. J. Occup. Environ. Health.* **2012**, *18* (2), 89-91.
171. Sustainable Impact | HP® Official Site. https://www8.hp.com/us/en/hp-information/global-citizenship/index.html. Accessed October 19, 2019.
172. Supplier Responsibility | Apple. https://www.apple.com/supplier-responsibility/. Accessed October 19, 2019.
173. Environment | Apple. https://www.apple.com/environment/. Accessed October 19, 2019.
174. Wolf, K. & Morris, M. Brake cleaning with water-based cleaning systems. *Pollut. Prevent. Rev.* **2000**, 13-30.
175. Centers for Disease Control and Prevention (CDC). n-Hexane-related peripheral neuropathy among automotive technicians--California, 1999-2000. *MMWR Morb. Mortal. Wkly. Rep.* **2001**, *50*, 1011-1013.
176. Wilson, M. P.; Hammond, S. K.; Nicas, M.; Hubbard, A. E. Worker exposure to volatile organic compounds in the vehicle repair industry. *J. Occup. Environ. Hyg.* **2007**, *4* (5), 301-310.

177. Yamada, S. An occurrence of polyneuritis by n-hexane in the polyethylene laminating plants. **1964**, *6*, 182.
178. Longnecker, M. P.; Rogan, W. J.; Lucier, G. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annu. Rev. Public Health.* **1997**, *18*, 211-244.
179. Haddad, L. M. Organophosphate insecticides. *Ann. Emerg. Med.* **1986**, *15*, 94.
180. Eskenazi, B.; Bradman, A.; Castorina, R. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ. Health Perspect.* **1999**, *107* (3), 409-419.
181. Steenland, K.; Jenkins, B.; Ames, R. G.; O'Malley, M.; Chrislip, D.; Russo, J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am. J. Public Health.* **1994**, *84* (5), 731-736.
182. Muñoz-Quezada, M. T.; Lucero, B. A.; Iglesias, V. P.; Muñoz, M. P.; Cornejo, C. A.; Achu, E.; Baumert, B.; Hanchey, A.; Concha, C.; Brito, A. M.; Villalobos, M. Chronic exposure to organophosphate (OP) pesticides and neuropsychological functioning in farm workers: a review. *Int. J. Occup. Environ. Health.* **2016**, *22* (1), 68-79.
183. Rubin, B. S. Bisphenol A: An endocrine disruptor with widespread exposure and multiple effects. *J. Steroid Biochem. Mol. Biol.* **2011**, *127* (1-2), 27-34.
184. Ji, K.; Hong, S.; Kho, Y.; Choi, K. Effects of bisphenol S exposure on endocrine functions and reproduction of zebrafish. *Environ. Sci. Technol.* **2013**, *47* (15), 8793-8800.
185. Viñas, R. & Watson, C. S. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. *Environ. Health Perspect.* **2013**, *121* (3), 352-358.
186. Catanese, M. C. & Vandenberg, L. N. Bisphenol S (BPS) alters maternal behavior and brain in mice exposed during pregnancy/lactation and their daughters. *Endocrinology.* **2017**, *158* (3), 516-530.
187. Doherty, R. E. A history of the production and use of carbon tetrachloride, tetrachloroethylene, trichloroethylene and 1,1,1-trichloroethane in the United States: Part 1–historical background; carbon tetrachloride and tetrachloroethylene. *Environ. Forensics.* **2000**, *1* (2), 69-81.
188. Doherty, R. E. A history of the production and use of carbon tetrachloride, tetrachloroethylene, trichloroethylene and 1,1,1-trichloroethane in the United States: Part 2–trichloroethylene and 1,1,1-trichloroethane. *Environ. Forensics.* **2000**, *1* (2), 69-81.
189. Lavoie, E. T.; Heine, L. G.; Holder, H.; Rossi, M. S.; Lee, R. E.; Connor, E. A.; Vrabel, M. A.; Difiore, D. M.; Davies, C. L. Chemical alternatives assessment: enabling substitution to safer chemicals. *Environ. Sci. Technol.* **2010**, *44* (24), 9244-9249.
190. Howard, G. J. Chemical alternatives assessment: the case of flame retardants. *Chemosphere.* **2014**, *116*, 112-117.
191. Geiser, K.; Tickner, J.; Edwards, S.; Rossi, M. The architecture of chemical alternatives assessment. *Risk Anal.* **2015**, *35* (12), 2152-2161.
192. National Academy of Sciences. A Framework to Guide Selection of Chemical Alternatives. **2014**.
193. CA Department of Toxic Substances Control. Alternatives Analysis Guide Version 1.0. **2017**.
194. National Research Council. Risk Assessment in the Federal Government: Managing the Process. **1983**.

195. U. S. EPA. National Air Toxics Assessment. **2015**.
196. Agency for Toxic Substances and Disease Registry. Toxicological profile for methylene chloride. **2000**.
197. Winek, C. L.; Collom, W. D.; Esposito, F. Accidental methylene chloride fatality. *Forensic Sci. Int.* **1981**, *18* (2), 165-168.
198. Wells, G. G. & Waldron, H. A. Methylene chloride burns. *Br. J. Ind. Med.* **1984**, *41* (3), 420.
199. Hall, A. H. & Rumack, B. H. Methylene chloride exposure in furniture-stripping shops: ventilation and respirator use practices. *J. Occup. Med.* **1990**, *32* (1), 33-37.
200. Moskowitz, S. & Shapiro, H. Fatal exposure to methylene chloride vapor. *AMA Arch. Ind. Hyg. Occup. Med.* **1952**, *6* (2), 116-123.
201. Stewart, R. D. & Hake, C. L. Paint-remover hazard. *JAMA* **1976**, *235* (4), 398-401.
202. Bonventre, J.; Brennan, O.; Jason, D.; Henderson, A.; Bastos, M. L. Two deaths following accidental inhalation of dichloromethane and 1,1,1-trichloroethane. *J. Anal. Toxicol.* **1977**, *1* (4), 158-160.
203. Bakinson, M. A. & Jones, R. D. Gassings due to methylene chloride, xylene, toluene, and styrene reported to Her Majesty's Factory Inspectorate 1961-80. *Occup. Environ. Med.* **1985**, *42* (3), 184-1190.
204. Manno, M.; Rugge, M.; Cocheo, V. Double fatal inhalation of dichloromethane. *Hum. Exp. Toxicol.* **1992**, *11* (6), 540-545.
205. Tay, P.; Tan, K. T.; Sam, C. T. Fatal gassing due to methylene chloride - a case report. *Singapore Med. J.* **1995**, *36* (4), 444-445.
206. Kim, N. Y.; Park, S. W.; Suh, J. K. Two fatal cases of dichloromethane or chloroform poisoning. *J. Forensic Sci.* **1996**, *41* (3), 527-529.
207. Estill, C. F.; Watkins, D. S.; Shulman, S. A.; Kurimo, R. W.; Kovein, R. J. Engineering controls for furniture strippers to meet the OSHA methylene chloride PEL. *AIHA J.* **2002**, *63* (3), 326-333.
208. Kelly, M. Case reports of individuals with oligospermia and methylene chloride exposures. *Reprod. Toxicol.* **1988**, *2* (1), 13-17.
209. Lash, A. A.; Becker, C. E.; So, Y.; Shore, M. Neurotoxic effects of methylene chloride: are they long lasting in humans? *Occup. Environ. Med.* **1991**, *48* (6), 418-426.
210. Taskinen, H.; Lindbohm, M. L.; Hemminki, K. Spontaneous abortions among women working in the pharmaceutical industry. *Occup. Environ. Med.* **1986**, *43* (3), 199-205 (1986).
211. Heppel, L. A.; Neal, P. A.; Perrin, T. L.; Orr, M. L.; Porterfield, V. T. Toxieology of dichloromethane (methylene chloride). I. studies on effects of daily inhalation. *J. Ind. Hyg. Toxicol.* **1944**, *26* (1), 8-16.
212. Haun, C. C.; Vernot, E. H.; Darmer, K. I.; Diamond, S. S. Continuous animal exposure to low levels of dichloromethane. Proceedings of the 3rd Annual Conference of Environmental Toxicology, October 25–27, **1972**.
213. Macewen, J. D. V. Continuous animal exposure to dichloromethane. NASA. **1972**.
214. Weinstein, R. S. & Diamond, S. S. Hepatotoxicity of dichloromethane (methylene chloride) with continuous inhalation exposure at a low dose level. Proceedings of the third Annual Conference on Environmental Toxicology 209-222, **1972**.
215. Morris, J. B.; Smith, F. A.; Garman, R. H. Studies on methylene chloride-induced fatty liver. *Exp. Mol. Pathol.* **1979**, *30* (3), 386-393.

216. Burek, J. D.; Nitschke, K. D.; Bell, T. J.; Wackerle, D. L.; Childs, R. C.; Beyer, J. E.; Dittenber, D. A.; Rampy, L. W.; McKenna, M. J. Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. *Fundam. Appl. Toxicol.* **1984**, *4* (1), 30-47.
217. Kjellstrand, P.; Bjerkemo, M.; Adler-Maihofer, M.; Holmquist, B. Effects of methylene chloride on body and organ weight and plasma butyrylcholinesterase activity in mice. *Acta. Pharmacol. Toxicol. (Copenh.).* 1986, **59**, 73-79.
218. National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). *Natl. Toxicol. Program Tech. Rep. Ser.* **1986**, *306*, 1-208 (1986).
219. Nitschke, K. D.; Burek, J. D.; Bell, T. J.; Kociba, R. J.; Rampy, L. W.; McKenna, M. J. Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats. *Fundam. Appl. Toxicol.* **1988**, *11* (1), 48-59.
220. Friedlander, B. R.; Hearne, T.; Hall, S. Epidemiologic investigation of employees chronically exposed to methylene chloride. Mortality analysis. *J. Occup. Med.* **1978**, *20* (10), 657-666.
221. Ott, M. G.; Skory, L. K.; Holder, B. B.; Bronson, J. M.; Williams, P. R. Health evaluation of employees occupationally exposed to methylene chloride. *Scand. J. Work Environ. Health.* **1983**, *9* (1), 1-38.
222. Lanes, S. F.; Rothman, K. J.; Dreyer, N. A.; Soden, K. J. Mortality update of cellulose fiber production workers. *Scand. J. Work. Environ. Health.* **1993**, *19* (6), 426-428.
223. U. S. EPA. Dichloromethane CASRN 75-09-2 | IRIS. **2019**.
224. Liu, T.; Xu, Q.; Zhang, C.; Zhang, P. Occupational exposure to methylene chloride and risk of cancer: a meta-analysis. *Cancer Causes Control.* **2013**, *24* (12), 2037-2049.
225. National Toxicology Program: 14th Report on Carcinogens. **2016**.
226. International Agency for Research on Cancer. Agents classified by the IARC Monographs. **2018**.
227. ACGIH. TLVs® and BEIs®-Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, **2001**.
228. NIH. Potassium hydroxide - National Library of Medicine HSDB Database. **2019**.
229. Vernot, E. H.; MacEwen, J. D.; Haun, C. C.; Kinkead, E. R. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. Appl. Pharmacol.* **1977**, *42* (2), 417-423.
230. Potassium hydroxide - Registration Dossier - ECHA. https://echa.europa.eu/registration-dossier/-/registered-dossier/15804/7/1. Accessed October 19, 2019.
231. Whittaker, M. H. Risk assessment and alternatives assessment: comparing two methodologies. *Risk Anal.* **2015**, *35* (12), 2129-2136.
232. Black, H. Chemical reaction: The U.S. response to REACH. *Environ. Health Perspect.* **2008**, *116*, A124-A127.